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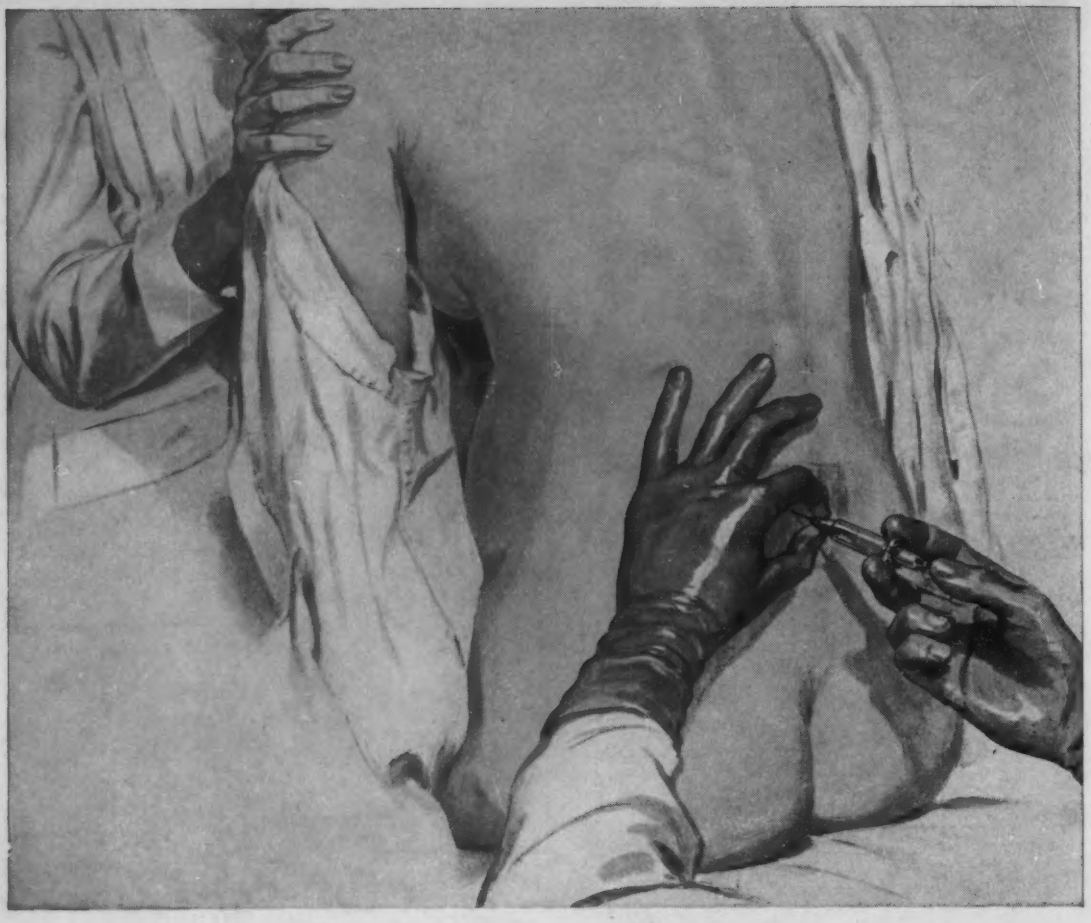

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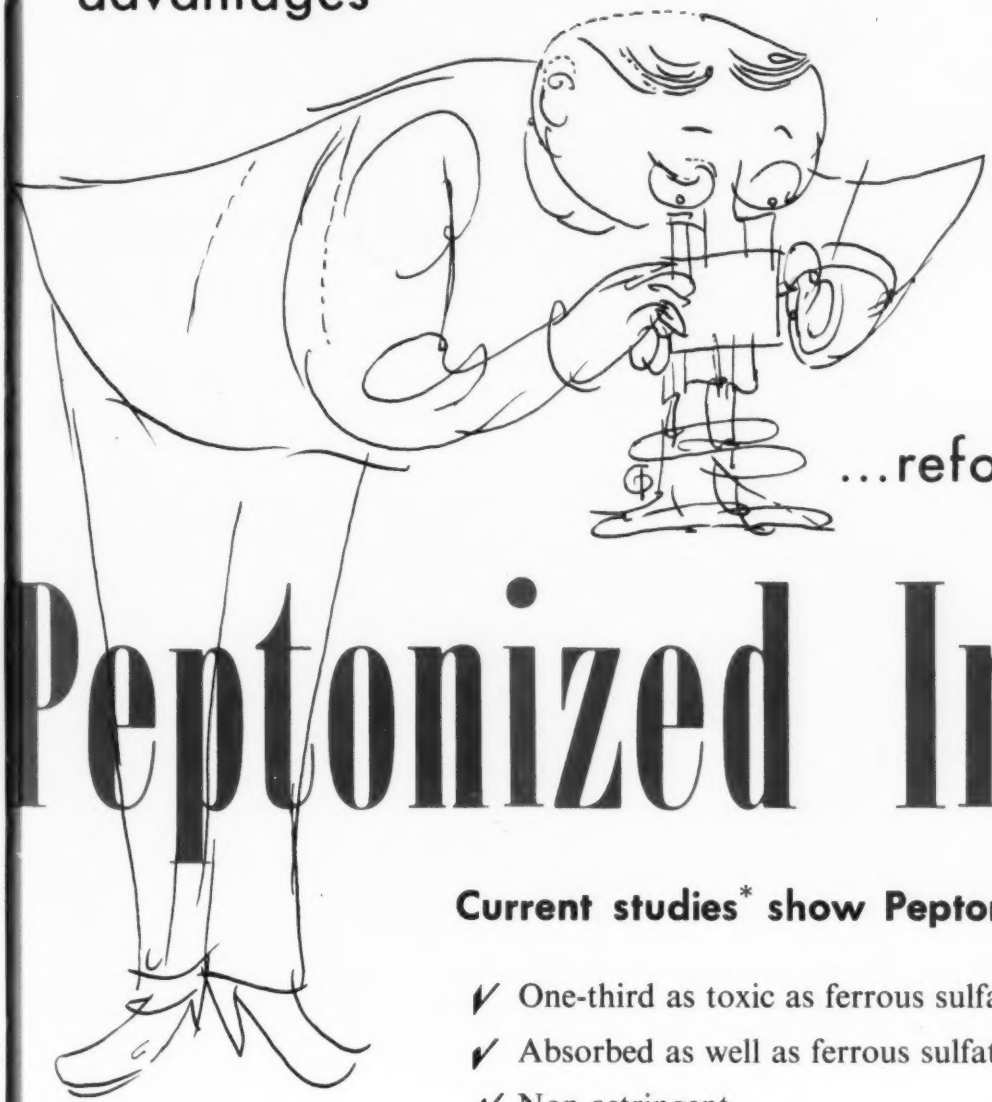

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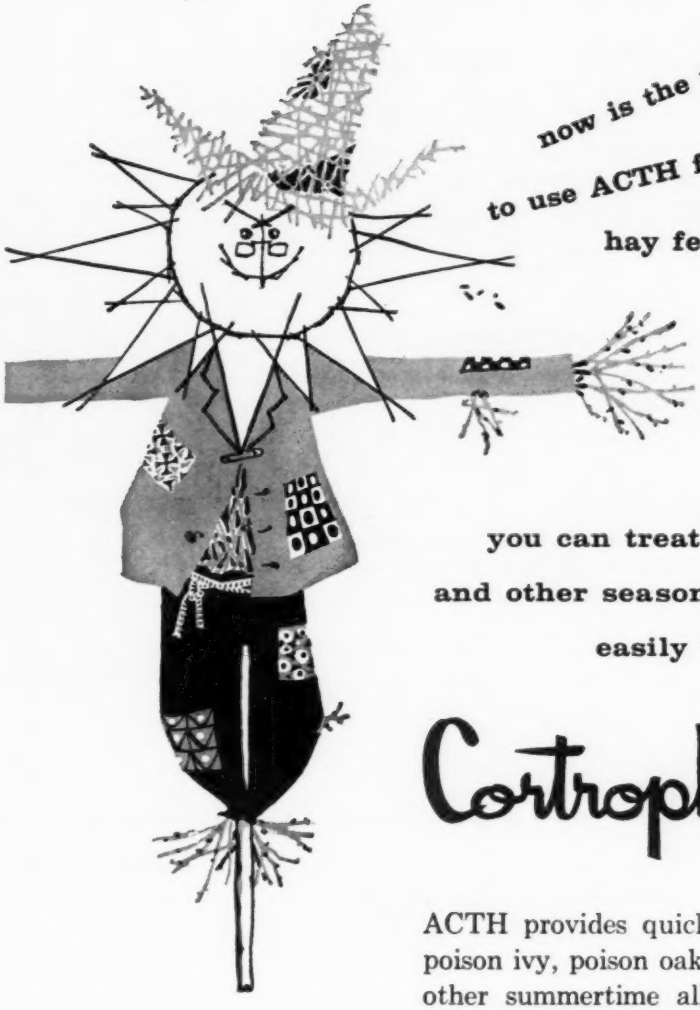

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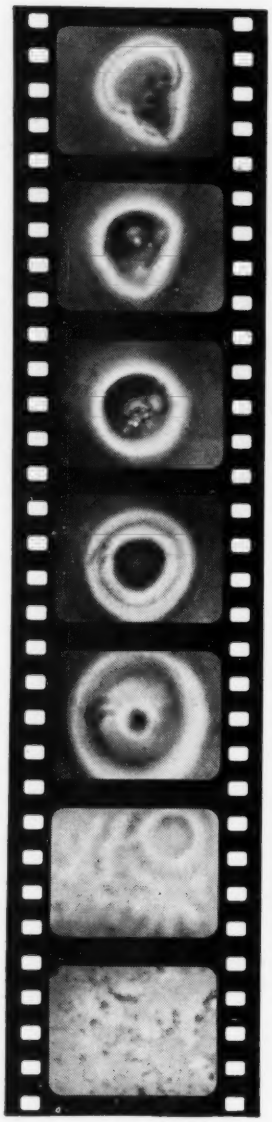

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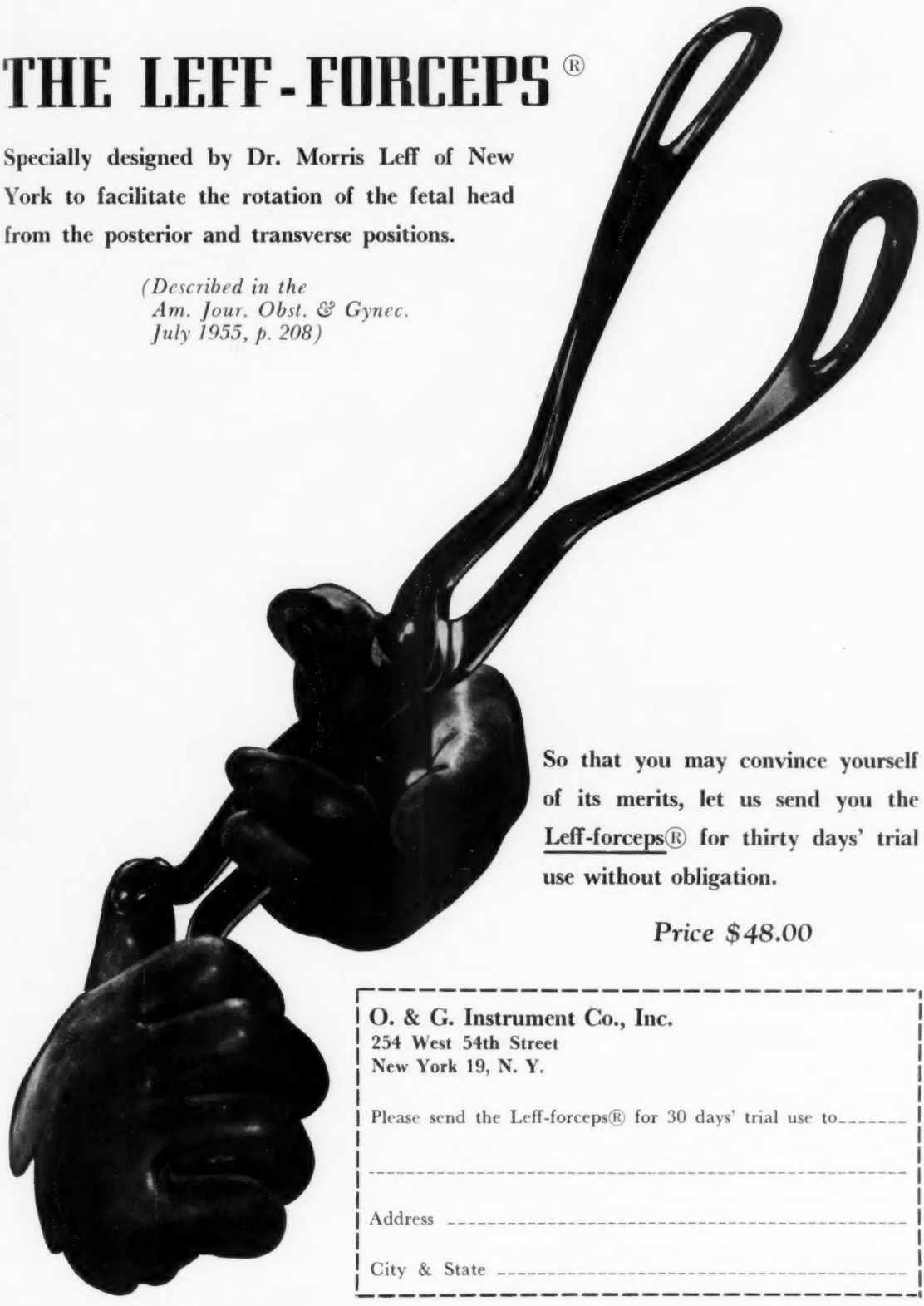

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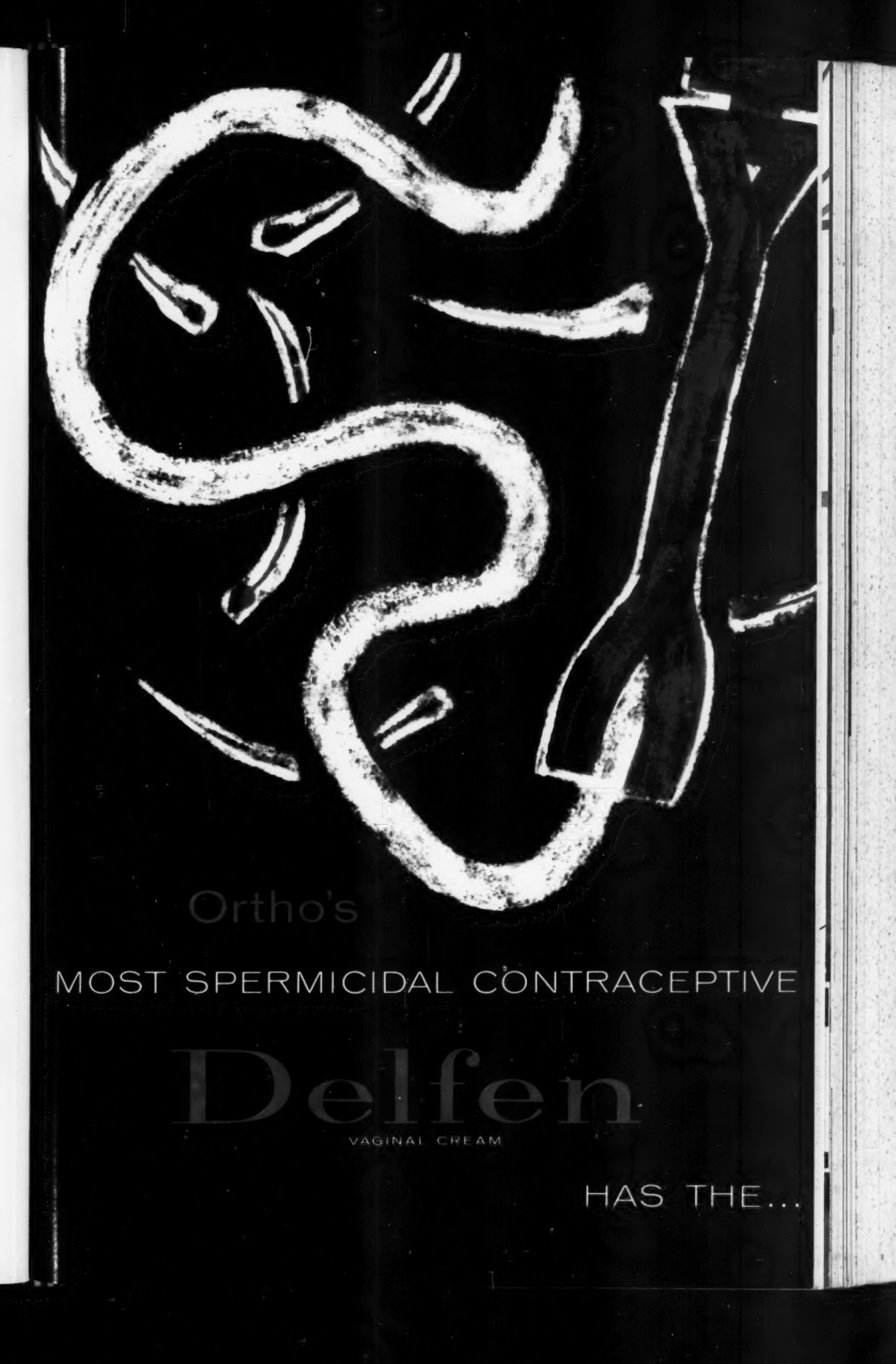
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1. Holt, L. E., Jr., and McIntosh, R.: Pediatrics, ed. 12, New York, Appleton-Century-Crofts, Inc., 1953, p. 12.
2. Kagan, B. M.; Hess, J. H.; Lundeen, E.; Shafer, K.; Parker, J. B., and Stigall, C.: Pediatrics *15*:373 (April) 1955.
3. Editorial: J. A. M. A. *159*:116 (Sept. 10) 1955.

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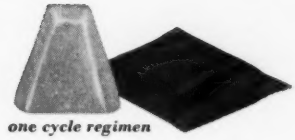

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*Schwartz, J.: Obst. Gyn. N. Y. 7:312, 1956.

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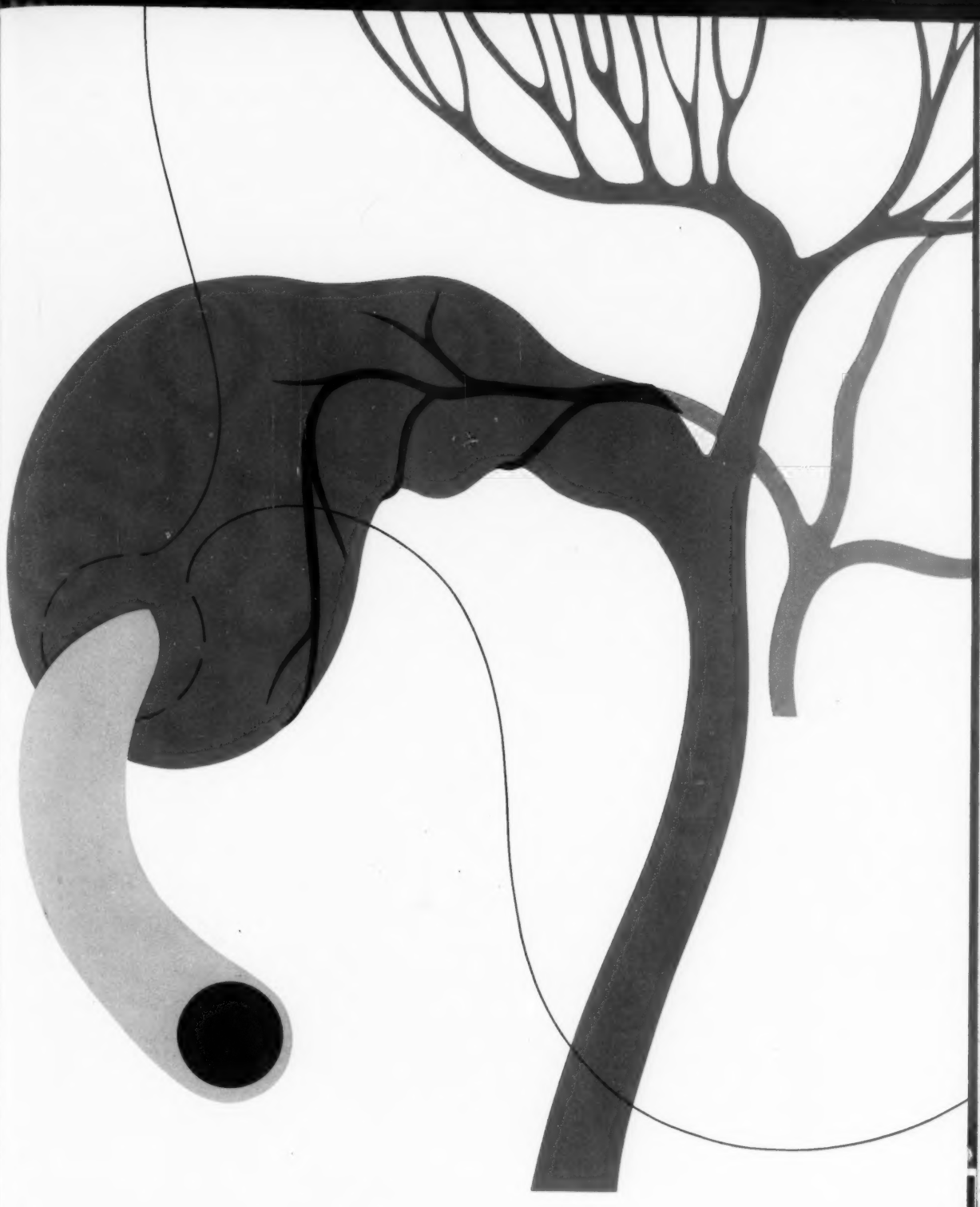

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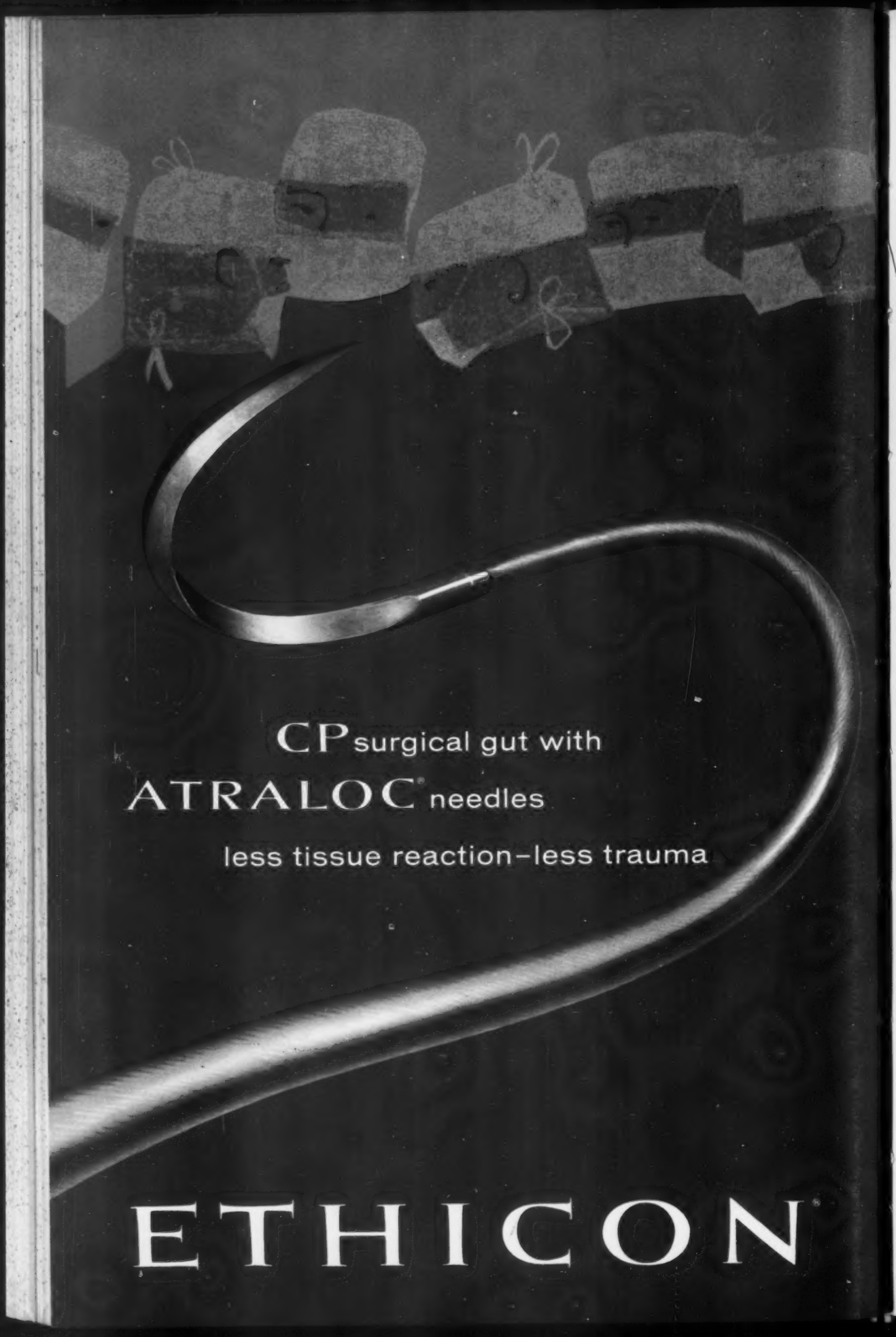
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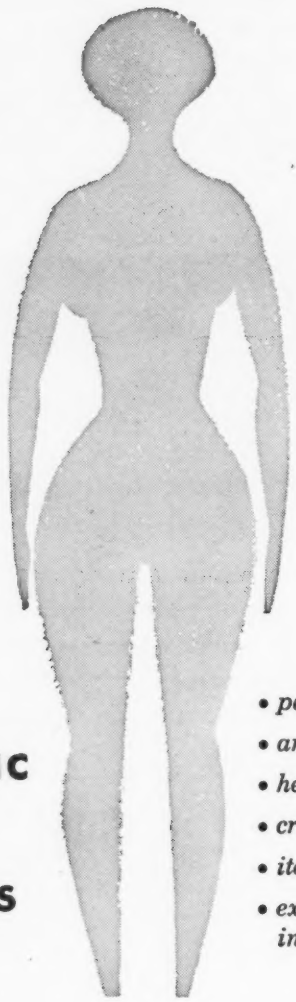

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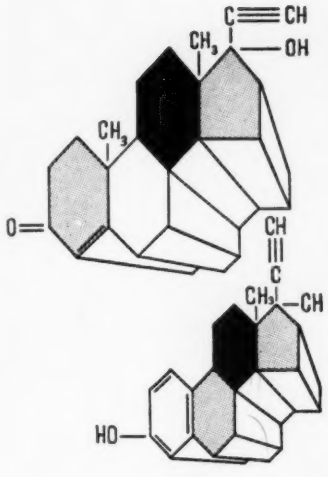

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*Am. J. Obst. & Gynec., 68:1321, 1954.

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1. Kloha, M.W.; Draper, M.D., and Keller, F.: Alkaloids of Rauwolfia Serpentina Benth. III. Rescinnamine, a New Hypotensive and Sedative Principle, J. Am. Chem. Soc. 76:2843 (1954).
2. Cronheim, G.; Brown, W.; Cawthorne, J.; Toekes, M.I., and Ungari, J.: Pharmacological Studies with Rescinnamine, a New Alkaloid Isolated from Rauwolfia Serpentina, Proc. Soc. Exper. Biol. & Med. 86:120 (May) 1954.
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5. Smirk, F.H., and McQueen, E.G.: Comparison of Rescinnamine and Reserpine as Hypotensive Agents, Lancet 2:115 (July 16) 1955.

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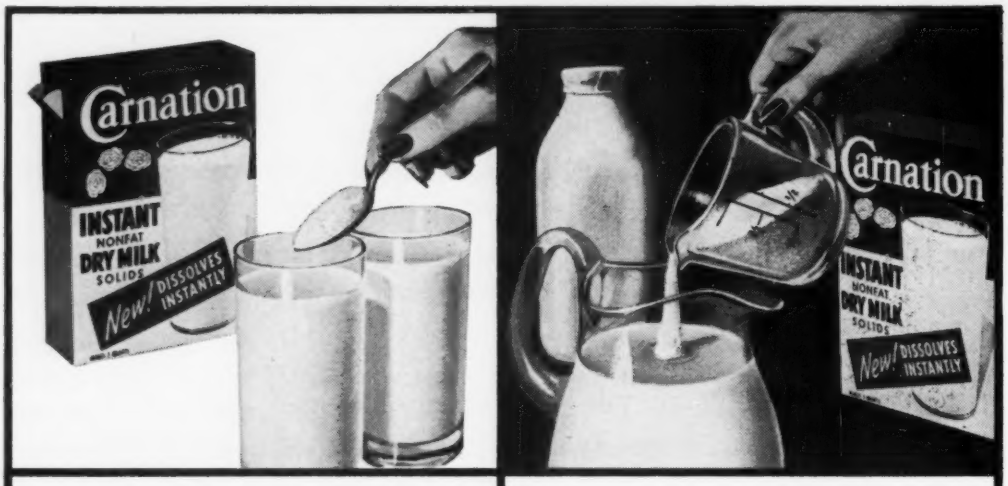

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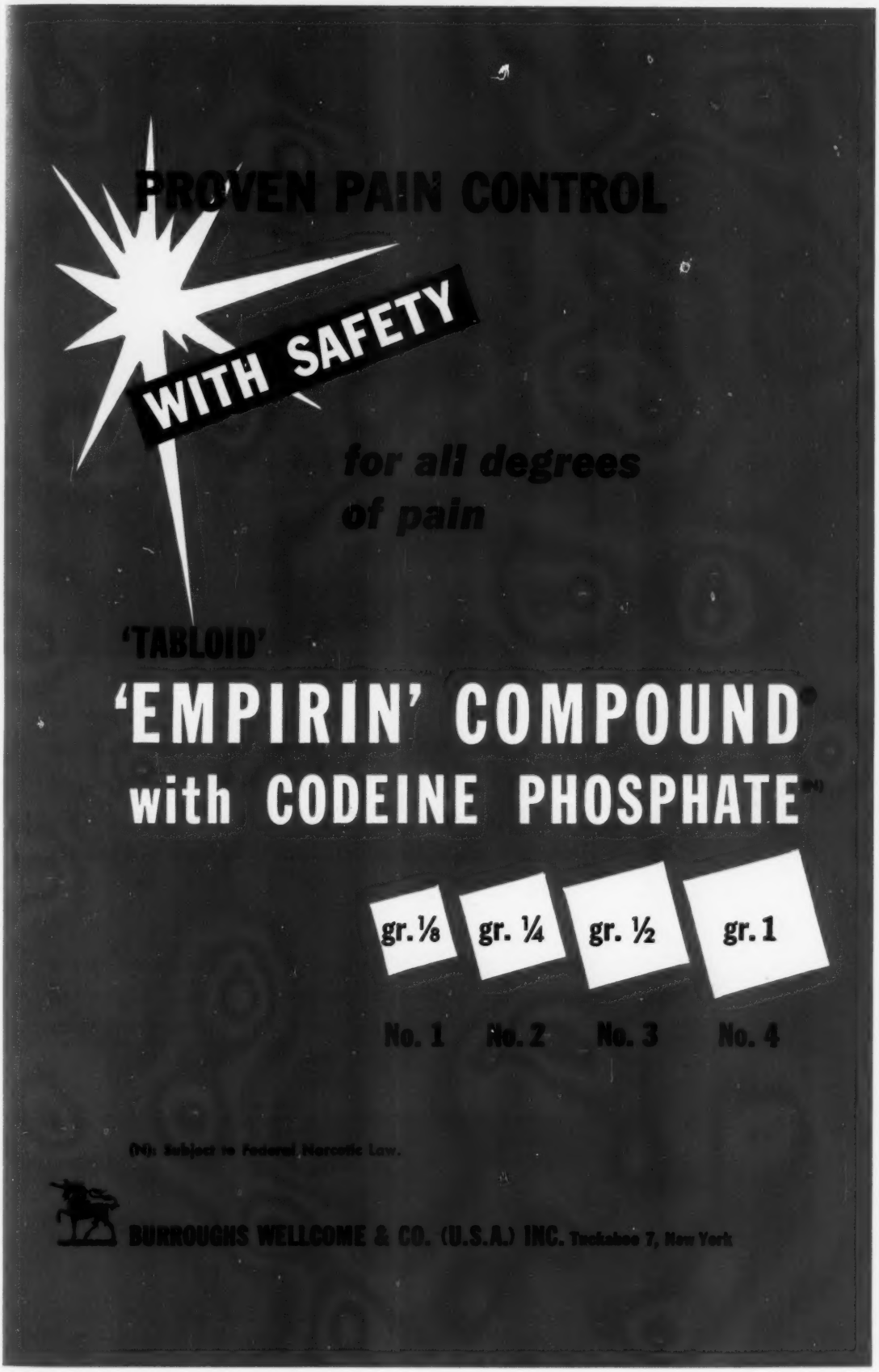
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The Use of the Systemic Hemostat Carbazochrome Salicylate

J. C. Bacala, M.D.

(Abstracted from the Western Journal of Surgery, Obstetrics, and Gynecology, 64:88 (1956)

The author emphasizes the need for dependable chemical control of bleeding and oozing, and reviews the methods that have been tried to attain hemostasis, including the use of vitamin K and bioflavonoids.

He gives the history of carbazochrome salicylate and describes the clinical work completed to demonstrate its effectiveness. It appears to be specific for conditions characterized by increased capillary permeability. It has no effect on large blood vessels; it does not alter blood components; it does not affect blood pressure or cardiac rate. It has neither vasoconstrictor or vasodilator action. The drug has no known contraindications.

He reviews 1051 cases from the files of St. Anthony Hospital, Louisville, Kentucky, of which 330 were treated with Adrenosem Salicylate. 317 were surgical cases and 13 obstetric-gynecological conditions. The treatment was given for symptomatic relief, and as a clinical recourse for patient safety.

In 1015 tonsillectomy patients the following results were noted: There was bleeding in 85 (19.8%) of 429 patients who received no medication. Patients who received a compound of oxalic and malonic acids numbered 115. Of these 16 (14%), developed bleeding. Of 248 patients receiving vitamin K preparations, 47 (19%) had postoperative hemorrhage. 233 patients received Adrenosem Salicylate. Of this group, only 16 (7%) had bleeding.

In other surgical conditions, Adrenosem was used successfully in gastrointestinal bleeding, cataract extraction, incisional seepage, and transurethral prostatectomy. It was also effective in 12 cases of epistaxis.

In the field of obstetrics and gynecology, Adrenosem controlled bleeding in menometrorrhagia, hymeneal laceration, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and in two cases of surgery during pregnancy.

The author points out that in pregnancy, seepage bleeding occurs more because of capillary permeability, and in spite of increased coagulability. Here, Adrenosem becomes specific for strengthening capillary resistance.

Many of the observations in this study, however, involved bleeding incident to trauma of incision, retraction, dissection, tearing and stretching. In these conditions, he reasons that Adrenosem causes hemostasis by its effect on the capillary intercellular cement substance so that the cells draw closer together, and the ends of the capillaries constrict, causing a "self-clamping" mechanism.

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The S. E. MASSENGILL company

BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

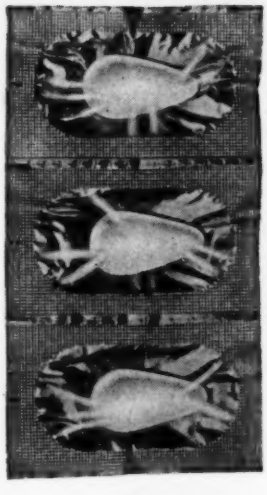
**U. S. Pat. 2581850*

for the treatment of

- **AMENORRHEA**
- **FUNCTIONAL UTERINE BLEEDING**
- **HABITUAL ABORTION**
- **LOBULAR HYPERPLASIA**
- **PREMENSTRUAL TENSION**

"colprosterone"®

Vaginal Progesterone



More acceptable
Avoids pain and inconvenience of injection . . . insures better patient cooperation than any other dosage form.

More dependable
Response is more predictable than with oral, or buccal and sublingual therapy.

More economical
Cost is low in terms of greater patient benefits.

"Colprosterone" Vaginal Tablets—Brand of progesterone U.S.P. presented in a specially formulated base to insure maximum absorption and utilization.

Complete dosage regimens for above indications are outlined in descriptive literature. Write for your copy.

Supplied: No. 793—25 mg. tablets (silver foil). No. 794—50 mg. tablets (gold foil). Boxes of 30 and Combination Package of 15 tablets with applicator.

Each tablet is individually and hermetically sealed. Presented in strips of 3 units, detachable as required.

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NEW **SEAMLESS** Lacta Pads

EFFICIENT AID IN POST-NATAL CARE...
A CONVENIENCE YOUR PATIENTS APPRECIATE

Hundreds of maternity departments have already adopted these wonderfully practical pads to solve the problem of excess lactation. Depend on your hospital to supply new Lacta Pads—an extra nicety that smooths your practice. Check these advantages:

WHY DOCTORS LIKE THEM

No pressure. Prevent retracted or cracked nipples. Reduce care.

Suited to professional technique. Ideal for applying medication.

Ideally designed and made to solve the excess lactation problem.

Assure greater patient comfort and satisfaction.

Samples promptly available on request. Simply jot it on your prescription form.

WHY PATIENTS LIKE THEM

Made of soft, non-irritating non-allergenic cotton. Highly absorbent and retentive.

Naturally, sensibly contoured. Full 3¾" in diameter.

Outside is non-absorbent; sealed circumference ring.

Full protection of clothing and appearance —no revealing lines.

Easy to insert without assistance. Disposable.

Surgical Dressings Division

THE SEAMLESS RUBBER COMPANY

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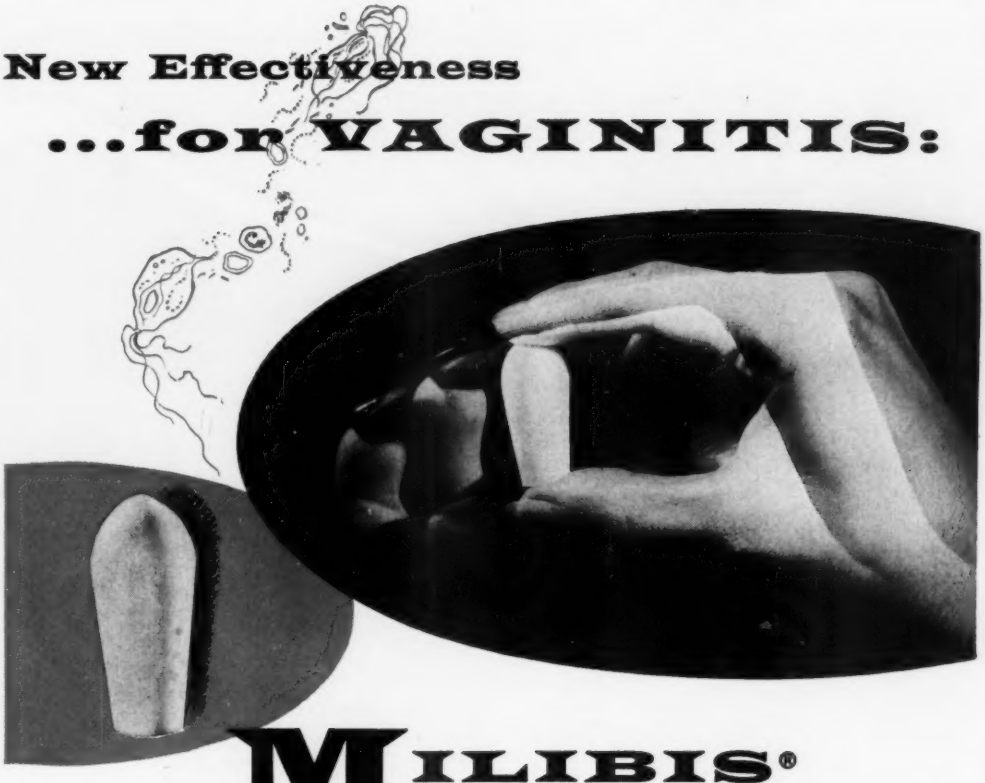
New Effectiveness
...for VAGINITIS:



MILIBIS®
Vaginal Suppositories

—soft and pliant as a tampon—white, odorless, non-staining—the suppositories bring new ease and new effectiveness to treatment of vaginitis.

SUPPLIED: BOXES OF 10

ELIMINATE SMEAR EXAMINATIONS*

Milibis vaginal suppositories are effective in trichomonad, Candida (monilia) as well as mixed and bacterial infections—thus laboratory identification of the offending organism is unnecessary.

THERAPEUTIC REGIMEN IS SHORT AND SIMPLE

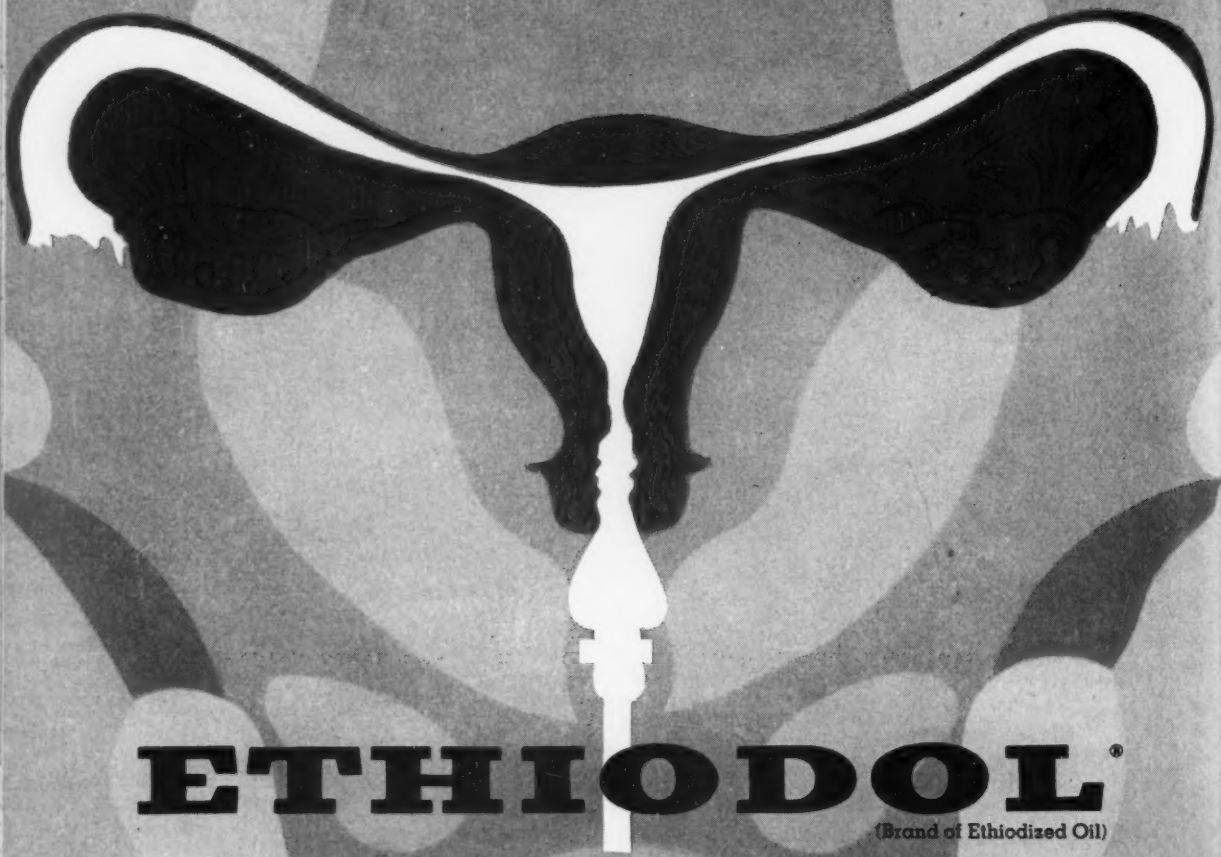
A total of only 10 suppositories (one inserted every other night) has given a remarkable rate of cure of over 90 per cent in two large series of cases. Milibis vaginal suppositories are easily inserted high into the vagina and form a tenacious film which coats the cervix and rugae, killing pathogens on contact. Non-staining, well tolerated.

*Except when gonorrheal infection is suspected.

Winthrop LABORATORIES New York 18, N.Y.

Milibis (brand of glycobiarsol), trademark reg. U.S. Pat. Off.

the advantages you want in hysterosalpingography...



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(Brand of Ethiodized Oil)

LIPIODOL® diagnostic with free-flowing viscosity

low viscosity for easier administration and free passage through narrow or strictured tubes or openings.

excellent radiopacity provides films as clear as with LIPIODOL for dependable diagnosis.

optimal absorption—completely absorbed usually within 45 days. Permits 24-hour film.

minimal patient discomfort—painless on contact with peritoneum. Bland, nontoxic and nonirritating.

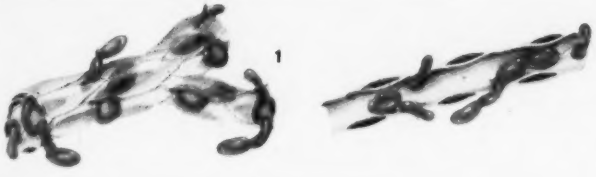
ETHIODOL, brand of ethiodized oil, is the ethyl ester of the iodinated fatty acid of poppyseed oil, containing 37% iodine. Available in 10-cc. ampules, boxes of two. A development of Guerbet Laboratories.

Literature available upon request.

FOUGERA **E. FOUGERA & COMPANY, INC** • 75 Varick Street, New York 13, N. Y.

95% FETAL SALVAGE

with HESPER-C



1 Red blood cells escaping from a capillary under abnormal conditions of capillary fragility.

2 Bleeding into the decidua basalis results from increased permeability of the uterine capillaries. The decidua then splits; a decidual hematoma is formed which leads to premature separation of the normally implanted placenta.

HESPER-C

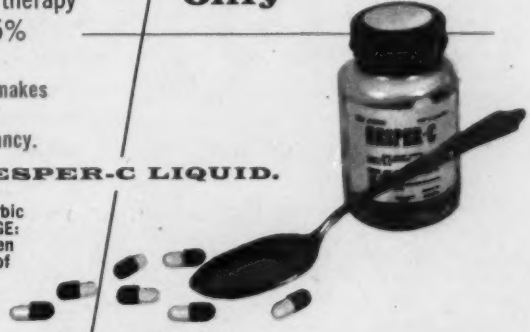
makes the difference

the original synergistic nutritional supplement for capillary fragility, is recommended as an integral part of any regimen for fetal salvage.[1] Maintaining capillary integrity during the critical months guards against abruptio placentae.[2] In 100 patients whose 420 previous pregnancies resulted in 95% fetal wastage, the addition of HESPER-C to current therapy completely reversed the figure and resulted in 95% fetal salvage.[3]

Remember Rx HESPER-C along with your usual therapy—it makes the difference.

Maintain the integrity of the capillaries throughout pregnancy.

on your prescription only



Now available, convenient New HESPER-C LIQUID.

HESPER-C provides hesperidin concentrate, 100 mg., and ascorbic acid, 100 mg., per capsule and per teaspoonful (5 ml.). DOSAGE: 6 capsules or teaspoonfuls or more per day for the first week. Then 4 capsules or teaspoonfuls daily. SUPPLIED: Liquid in bottles of 4 oz. and 12 oz. Capsules in bottles of 100 and 1000.

REFERENCES: 1. Dill, L. V.: Med. Ann. of D. of C., 23:667, 1954. 2. Greenblatt, R. B.: Obst. and Gyn., 2:530, 1953. 3. Javert, C. T.: Obst. and Gyn., 3:420, 1954,

The film "CLINICAL ENZYMOLOGY" is now available for showing at medical meetings upon your request. And be sure to watch for the MED-AUDIOGRAPHS, a series of recorded clinical discussions.

PRODUCTS OF ORIGINAL RESEARCH

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THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.

The CLASSICAL *Vaginal Therapeutic*

UNIQUE WITH 9-AMINOACRIDINE,

the nonirritating, broad-spectrum, stable bactericidal agent. Effective where organisms have become resistant to other drugs.

AVC Improved has been accepted, and in ever-expanding use for over 12 years, as the most comprehensive therapy in:

Trichomonal Leukorrheas • Monilial and Nonspecific Vaginitis • Cervicitis • Postpartum Hygiene • Pre- and Postcauterization, Coagulation, Conization and other Vaginal Surgery

AVC Improved provides: Broad-spectrum, sustained vaginal pathogen killing power because the remarkable synergism of 9-aminoacridine and sulfanilamide effects the actual destruction of the inhibitors of maximum bactericidal action. Surface-active, spreading, penetrating agent; buffered vaginal pH; nutrient for normal vaginal flora; mucus digestion; immediate relief of odor and itching; restoration of vaginal mucosa, by actively promoting tissue repair and granulation.

AVC Improved is a cream containing 0.2% 9-Aminoacridine Hydrochloride, 15% Sulfanilamide, 2% Allantoin, in a water-miscible base buffered to approximately pH 4.5.

SUPPLIED: 4 oz. tubes with or without applicator. ADMINISTRATION: An applicatorful of AVC Improved should be introduced high in the vagina twice daily, upon arising and at bedtime.

PRODUCTS OF ORIGINAL RESEARCH

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THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.

New urethral suppositories relieve pain and fight infection

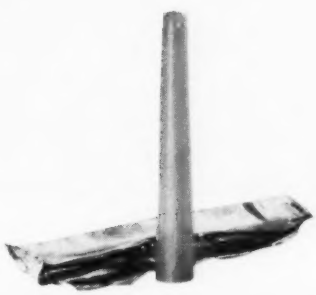
For the patient, "The treatment is shorter and more comfortable than with the conventional method..."*

- suppository melts and releases anesthetic agent to relieve pain and burning *rapidly*
- kills most bacteria common to urinary tract
- easy for patient to insert at home
- *safe*—irritation rare in over 340 reported cases*
- *proved*—"The suppository method of medication has proved its worth."*. . . in bacterial (granular) urethritis; for prophylaxis and pain-relief before and after instrumentation.

to prevent cross-infection...

FURACIN® vaginal Suppositories are used with Furacin Urethral Suppositories to prevent cross-infection from the vagina. Hermetically sealed in yellow foil. Box of 12.

*Youngblood, V. H.: J. Urol. *70*:926, 1953.



FURACIN®
BRAND OF NITROFURAZONE
urethral
SUPPOSITORIES

Each Furacin Urethral Suppository contains 0.2% Furacin (brand of nitrofurazone) and 2% diperodon HCl in a water-miscible base. Hermetically sealed in silver foil. Box of 12.

EATON LABORATORIES, Norwich, N.Y. **NITROFURANS** a new class of antimicrobials neither antibiotics nor sulfas

To have and to hold... in sickness and in *health.* ➢ How richer the union when the wife is blessed with radiant health... how much more capable she is of serving her family, her community! ➢ More and more the physician is the guide and mentor, the preserver of family well-being... particularly in his advice to husbands and wives on scientific methods of child-spacing. Because of the doctor's knowledge, skill, and experience, healthful parenthood goals are being achieved ... earning for the doctor respect for his judgment and gratitude for this contribution to richer family life, through his recommendation of—*Koromex*

AVAILABLE AT ALL LEADING PHARMACIES • KOROMEX JELLY, CREAM AND DIAPHRAGM COMPACT
HOLLAND-RANTOS COMPANY, INC. • 145 HUDSON STREET • NEW YORK 13, N. Y.

In deference to her daintiness . . .

- Massengill Powder is buffered to *maintain** an acid condition in the vaginal mucosa.
- Massengill Powder has a low surface tension which enables it to penetrate into and cleanse the folds of the vaginal mucosa.
- Massengill Powder has a "clean" antiseptic fragrance. It enjoys unusual patient acceptance.
- Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

massengill powder®

when recommending a vaginal douche

indications:

Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Routine douching with Massengill Powder solutions minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

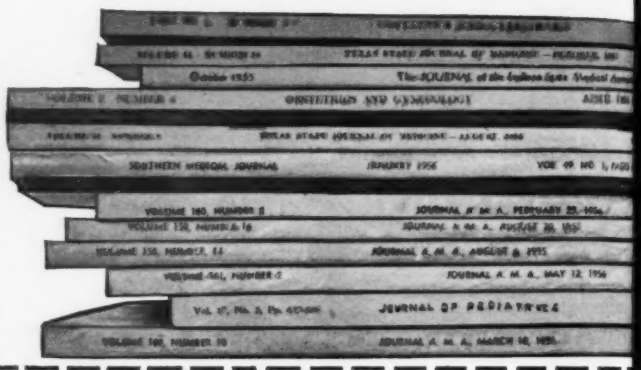
*In a recent clinical report, ambulatory patients—with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours.

Generous samples on request.

The S. E. MASSENGILL Company

Bristol, Tennessee *New York* *Kansas City* *San Francisco*

"...THE MOST EFFECTIVE HEMATINIC..."*



The convincing evidence supporting the unique and advanced concept of cobalt-iron therapy in anemia is based on RONCOVITE research.

Roncovite is the only clinically proved preparation supplying cobalt in the therapeutic levels essential for the optimal hematologic response in anemia. The presence of cobalt as a specific bone marrow stimulant improves the utilization of iron and makes Roncovite totally different from any other hematinic preparation.

The safety and potency of Roncovite has been repeatedly confirmed.

Your own results will show why "The bibliography specifies RONCOVITE."

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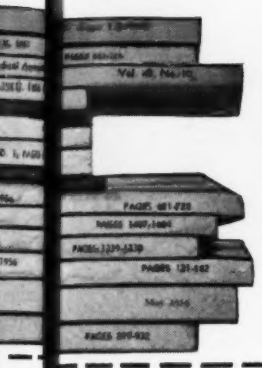

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—THE ORIGINAL CLINICALLY PROVED COBALT-IRON PRODUCT—

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when one is watching weight for two...

She's a problem sometimes, isn't she? Even if she knows that eating for two means quality, not quantity, she's just not always sure what quality implies. When she gets hungry enough for two, she can't always be logical about it. And she can rationalize that extra gain so easily, with one eye on the calendar.

Fortunately for today's expectant mother, weight-watching can be much easier . . . with *Instant* Pet Nonfat Dry Milk.

She can reconstitute it for drinking, and enjoy delicious fresh-milk flavor with all milk's protein, calcium, and B-vitamins—but only half the calories of whole milk. She can use *Instant* Pet, in either liquid or dry form, to cut calories in cooking. And the addition of extra *Instant* Pet, in dry form, to some of her favorite dishes can greatly increase needed calcium and protein intake without appreciably increasing calories.

When she has *Instant* Pet's help in her weight-watching for two, she's a lighter load on your scales, less of a problem for you.

Instant PET NONFAT DRY MILK
supplies essential milk nourishment with minimum caloric intake at minimum cost.

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What does it take to make a drug a classic?

It doesn't just happen. In the case of PENTOTHAL Sodium, twenty years of experience are behind its present unchallenged position. Twenty years in which the knowledge gained from its use in millions of patients, and the information published in over 2,500 scientific papers, has been constantly supplemented with improvements and refinements in its manufacture.

PENTOTHAL Sodium is not merely thiopental sodium . . . it is thiopental sodium *plus* the most rigorous and exacting controls . . . *plus* the most thoughtfully planned dosage forms . . . *plus* the finest manufacturing techniques. These are the *priceless pluses* that belong to a drug only when *experience* has been added to thought and care.

Pentothal® Sodium
(Thiopental Sodium, Abbott)

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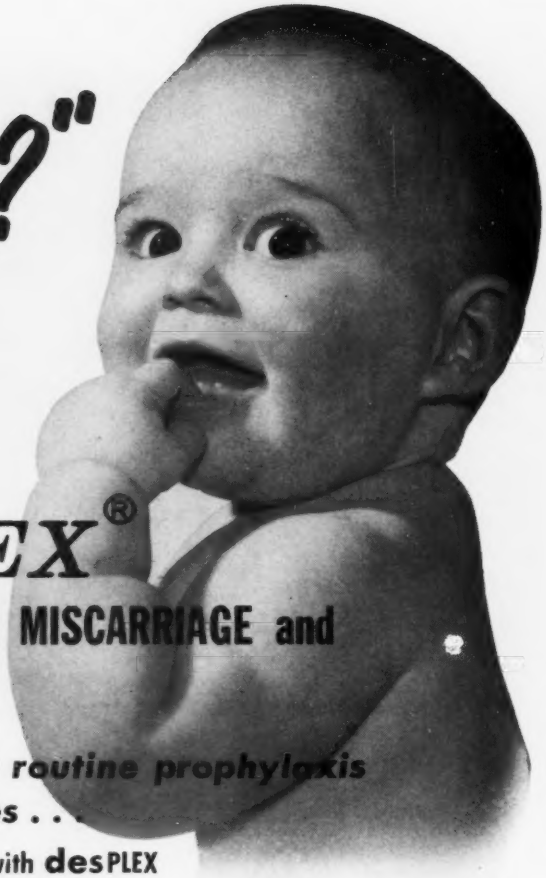
"Really?"



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desPLEX®

to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR

recommended for routine prophylaxis in ALL pregnancies . . .

96 per cent live delivery with desPLEX in one series of 1200 patients[4]— — bigger and stronger babies, too.[cf. 1]

No gastric or other side effects with desPLEX — in either high or low dosage[3,4,5]

(Each **des**PLEX tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating *to assure prompt help in emergencies.* **des**PLEX tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

For further data and a generous trial supply of **des**PLEX, write to:
Medical Director

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5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.

this is the couple

completely cured

by Ortho's new oral....

new oral trichomonacide

TRITHEON® TABLETS

BRAND OF AMINITROZOLE

for male and female

Because of their systemic action, TRITHEON tablets reach resistant trichomonads in their hiding places throughout the genitourinary tract. Unlike local trichomonacides, TRITHEON tablets eradicate the organism in male and female as proved by *negative culture*.

Clinical investigation has demonstrated that TRITHEON tablets administered orally eradicate trichomonads for **culture-proved cure** of more than 70 per cent of female patients whose husbands are treated simultaneously with TRITHEON tablets. Even when only the wife is treated, cures are effected in approximately one-third of the patients.

Ortho

Dosage: One tablet three times daily for 10 days.

Available: Bottles of 30 and 180 tablets.

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a new measure in therapy of overweight

PRELUDIN®

(brand of phenmetrazine hydrochloride)

...reduces risk in reducing

A totally new development in anorexigenic therapy, PRELUDIN substantially reduces the risks and discomfort in reducing.

Distinctive in its Chemistry: PRELUDIN is a totally new compound of the oxazine series.

Distinctive in Effectiveness: In three years of clinical trials PRELUDIN has consistently demonstrated outstanding ability to produce significant and progressive weight loss through voluntary effortless restriction of caloric intake.

Distinctive in Tolerance: With PRELUDIN there is a notable absence of palpitations or nervous excitement. It may generally be administered with safety to patients with diabetes or moderate hypertension.

For your patient's greater comfort: PRELUDIN curtails appetite without destroying enjoyment of meals...causes a mild evenly sustained elevation of mood that keeps the patient in an optimistic and cooperative frame of mind.

Recommended Dosage: One tablet two or three times daily taken one hour before meals. Occasionally smaller dosage suffices.

PRELUDIN® (brand of phenmetrazine hydrochloride). Scored, square, pink tablets of 25 mg.
Under license from C. H. Boehringer Sohn, Ingelheim.

GEIGY PHARMACEUTICALS
Division of Geigy Chemical Corporation • Ardsley, N.Y.

GEIGY

Safety First | in control of Nausea of Pregnancy

The first thought of every physician during the prenatal period is the safety of the patient.

The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
2. EMETROL has been shown to be effective in nausea and vomiting in controlled clinical studies.[1-3]
3. EMETROL is so palatable that most patients will take it readily.
4. EMETROL works quickly, often bringing relief with the first dose.

SAFE

EMETROL®

(Phosphorated Carbohydrate Solution)

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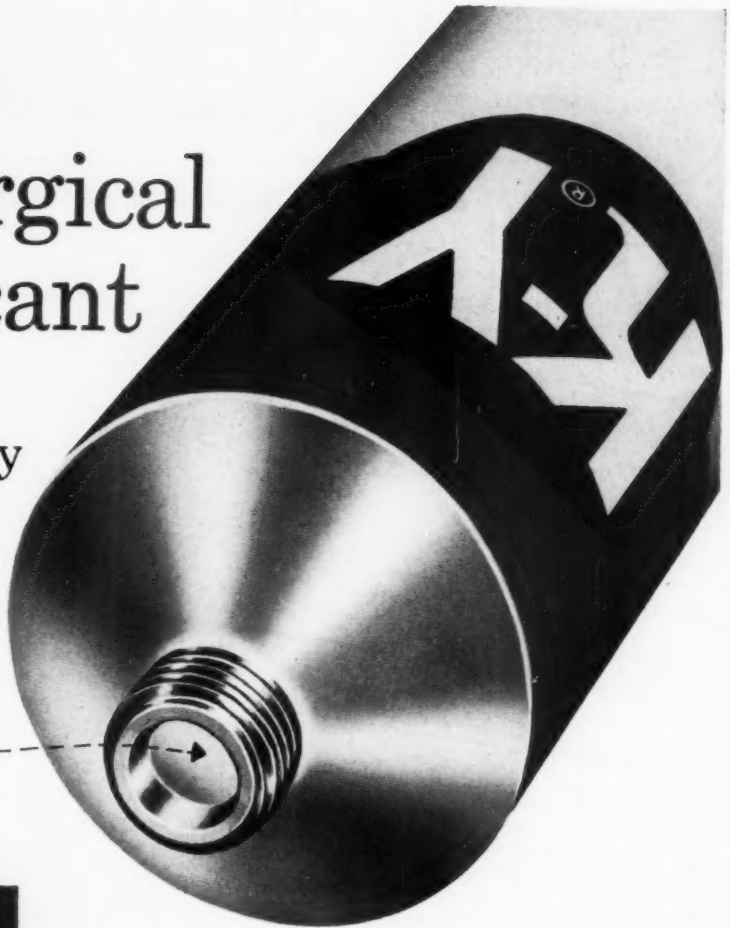
the surgical lubricant

hermetically sealed to guarantee sterility



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STERILE LUBRICANT

greaseless
harmless to rubber
non-irritating
water soluble
transparent

Johnson & Johnson

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how Pambromal relieves premenstrual tension—

(FROM AN ACTUAL CASE HISTORY)

CASE HISTORY

NAME L.W. AGE 31 y. SEX F. MARITAL STATUS Married

DATE 1/25/55

DIAGNOSIS Alimentary obesity on emotional basis.

COMPLAINTS Obesity. Moderate dysmenorrhea. Premenstrual tension with bloating.

PHYSICAL EXAMINATION Negative.

THERAPY Placed on 1000 calorie diet. D-amphetamine. Thyroid. Pambromal tablets (2 to 3 tabs. a day) to be taken 1 week before menses.

Striking relief from all premenstrual symptoms. Patient stated that it was the first time that she had had any relief from her premenstrual symptoms.

FOLLOW-UP 10/27/55. Lost 35 lbs. No complaints.

WHITTIER LABORATORIES • CHICAGO 11, ILLINOIS Whittier

COMMENT:

The premenstrual tension syndrome, in many instances, is an incidental complaint. The patient often consults the physician for some unrelated disease. In spite of the emotional problems it creates, quite a few patients may forget mentioning their distress unless specifically asked for the symptoms.

Now, relief can be given and it is deeply appreciated...

PAMBROMAL *neutralizes the antidiuretic hormone*

	subject 1	subject 2	subject 3
Diuresis without pamabrom	106 cc.	275 cc.	210 cc.
Diuresis with pamabrom (100 mg.)	950 cc.	980 cc.	1200 cc.

Subjects were given 1000 cc. of water and injected with antidiuretic hormone (pitressin). When pamabrom (an ingredient of Pambromal) was administered, the water-retaining effect of the antidiuretic hormone was almost completely neutralized.

(Bickers, W., and Wood, M.: New England J. Med. 240: 453, 1951)

PAMBROMAL *controls nervous system lability*

Contains both dextro-amphetamine sulfate and carbromal, a reliable sedative...counteracts irritability, anxiety and fatigue...relaxes tensions.

PAMBROMAL *relieves pain more effectively*

Contains salicylamide—a time-tested and proven analgesic considerably more potent than other salicylates.

Each tablet contains:
Pamabrom (to neutralize the antidiuretic hormone) .....50 mg.
Dextro-amphetamine sulfate (to elevate mood).....2.5 mg.
Carbromal (to relax tension)...130 mg.
Salicylamide (to relieve pain)..250 mg.
Bottles of 24 and 100

PAMBROMAL®
tablets

Ultraviolet therapy

proving of high clinical value in treatment of pregnant and nursing mothers

LUXOR ALPINE QUARTZ LAMP
Delivers complete ultraviolet spectrum. Provides intense radiation of wide, even distribution.
Newly designed professional model. HANOVIA ALPINE ULTRA-VIOLET QUARTZ LAMP Precision built. Exceptionally mobile. Very moderately priced.
To be prescribed by you for home use. NEW FULL-SPECTRUM QUARTZ HEALTH LAMP, ULTRA-VIOLET *plus* INFRARED—MODEL 55 Light, compact, easy to use. Safe-T-Timer. Moderately priced.

Prenatal Hanovia Ultraviolet irradiation of the mother, and irradiation of the nursing mother, have definite preventive influence on rickets. In care of infants, the prophylactic and curative effects of ultraviolet radiation on rickets, infantile tetany or spasmophilia, and osteomalacia are well known.

Important, too, is the value of ultraviolet therapy as a proven valuable ancillary treatment in physical rehabilitation. Authoritative report reads: "The blood changes produced in ultraviolet radiation are increased number of red and white cells and platelets, lowered blood sugar, increased sugar tolerance, increased blood calcium, relative lymphocytosis and eosinophilia."

In addition to your office use of ultraviolet equipment, ease your schedule by prescribing home ultraviolet therapy, yet maintain treatments under your control. New Hanovia Health Lamp Model 55, prescribed by you, may be purchased from surgical supply dealers.

Yours On Request: Valuable authoritative treatise describing ultraviolet in obstetrics and pediatrics. Without obligation, write for your free copy. Dept. OG-9

World-Leader in Ultraviolet for Over 50 Years. Hanovia scientists and engineers have made major contributions to the vast improvement in physical therapy equipment, keeping pace with modern science and clinical requirements.

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vitamin-mineral combination

Since optimum nutrition is important to the well-being of women in pregnancy and during lactation, dietary supplementation is frequently indicated. By providing essential vitamins, the intrinsic factor, iron, and calcium, NATABEC Kapseals contribute to better present and future health for the obstetrical patient and her child.

dosage: As a dietary supplement during pregnancy and lactation, one or more Kapseals daily as directed by the physician. Available in bottles of 100 and 1,000.

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3 oz. tube of Lanteen jelly.
New Easy-clean jelly applicator.
Lanteen flat spring diaphragm of prescribed size.
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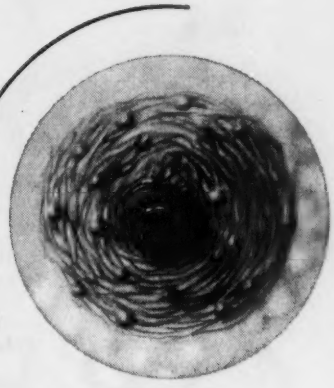
Physician's prescription package.

*Lanteen jelly contains ricinoleic acid 0.50%, hexylresorcinol 0.10%, chlorothymol 0.0077%, sodium benzoate and glycerin in a tragacanth base. Lanteen jelly and flat-spring diaphragm sets are distributed by George A. Breon & Company, 1450 Broadway, New York 18, N. Y. (In Canada: E. & A. Martin Research Ltd., 20 Ripley Ave., Toronto, Canada.) Manufactured by Esta Medical Laboratories, Inc., Chicago 38, Ill. *Trademark of George A. Breon & Company.*



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The use of White's Vitamin A & D Ointment soothes and softens the fissured nipple, promotes tissue regeneration.

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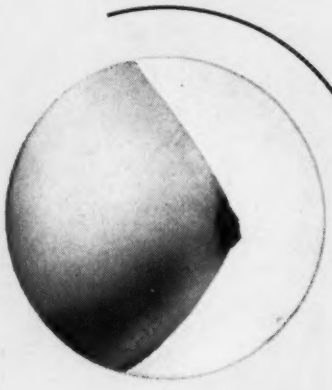

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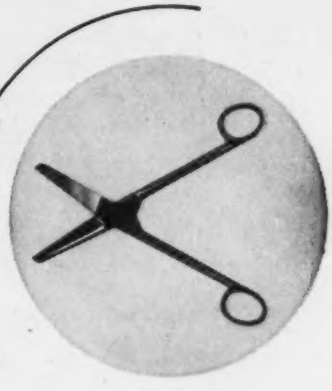

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Specify White's Vitamin A & D Ointment also in such conditions as burns, diaper rash, chafing, indolent ulcers.
Recommend the 1½ or 4 oz. tubes; the 1 lb. or 5 lb. jars.

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In proper dosage, prevents or reverses narcotic-induced respiratory depression *without* inhibiting pain relief

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Acts for 2 to 5 hours

One mg is equivalent to at least 5 mg nalorphine

Lorfan will counteract the depressant effects of synthetic narcotics such as Levo-Dromoran,® Nisentil,® meperidine, methadone, as well as the natural opiates – morphine, dihydromorphinone, Pantopon®. May be used in combination with narcotics for preoperative preparation, postoperative pain, supplementation of nitrous oxide-oxygen anesthesia, obstetrics.

Lorfan™ Tartrate – brand of levallorphan tartrate

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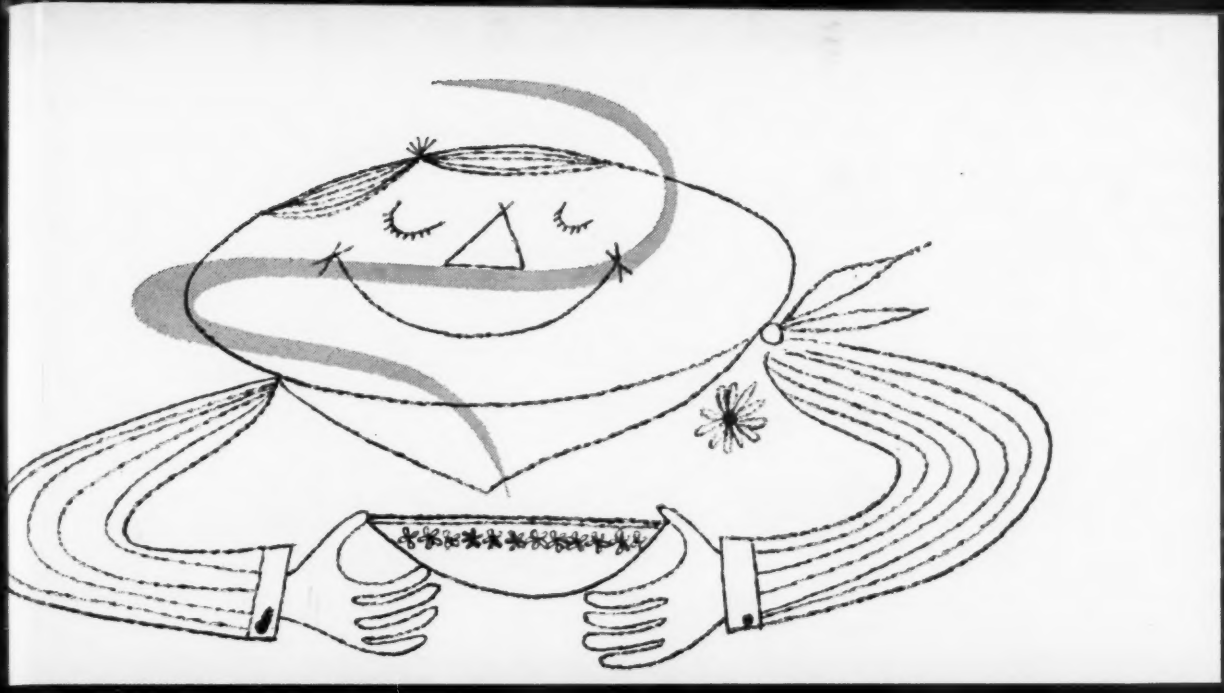

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THE PLANNED BIG FAMILY

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1. U. S. Government figures.
2. College Study Report: Population Bulletin *11*:45 (June) 1955.
3. Tietze, C., in Dickinson, R. L.: Techniques of Conception Control, ed. 3, Baltimore, Williams & Wilkins Co., 1950, pp. 55-57.

*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

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A simple non-toxic, non-staining vaginal douche, Triva disintegrates microbes. Its powerful detergent surface-active agent, plus a chelating agent, annihilates organisms and flushes them away.

SAFE . . . even during pregnancy, Triva has been proved, by clinical tests, highly effective against Trichomonal, Monilial and non-specific vaginitis. Simple to prescribe: "TRIVA (Boyle) sig; douche b.i.d. for 12 days." For complete data see Physicians' Desk Reference, 1956, page 427.

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Full treatment package and literature on request.

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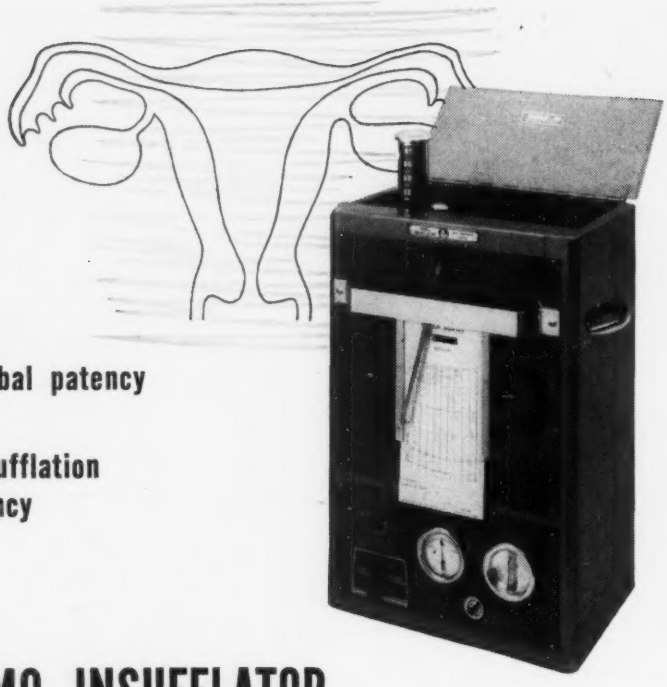

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or repeating insufflation
to improve patency

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a *new* class of antimicrobials
neither antibiotics nor sulfonamides

Average dose: one 100 mg. tablet, q.i.d.; 1 tablet with each meal and 1 with food or milk on retiring.

Tablets: 50 and 100 mg., bottles of 25 and 100.

References: 1. Kass, E. H.: Am. J. Med. 18:764, 1955. 2. Diggs, E. S., Prevost, E. C., and Valderas, J. G.: Am. J. Obst. 71:399, 1956.

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Supplied in 1½ oz. tube with 6 disposable applicators. Instructions for use are included with each package.

*Gardner, H. L., and Dukes, C. D.: Am. J. Obst. & Gynec. 69:962 (May) 1955.

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she deserves
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for immediate and
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Each capsule contains: Pyridoxine hydrochloride—50 mg.; dl-Methionine—100 mg.; Nicotinamide—25 mg.; Pentobarbital sodium—15 mg.; Benzocaine—100 mg.

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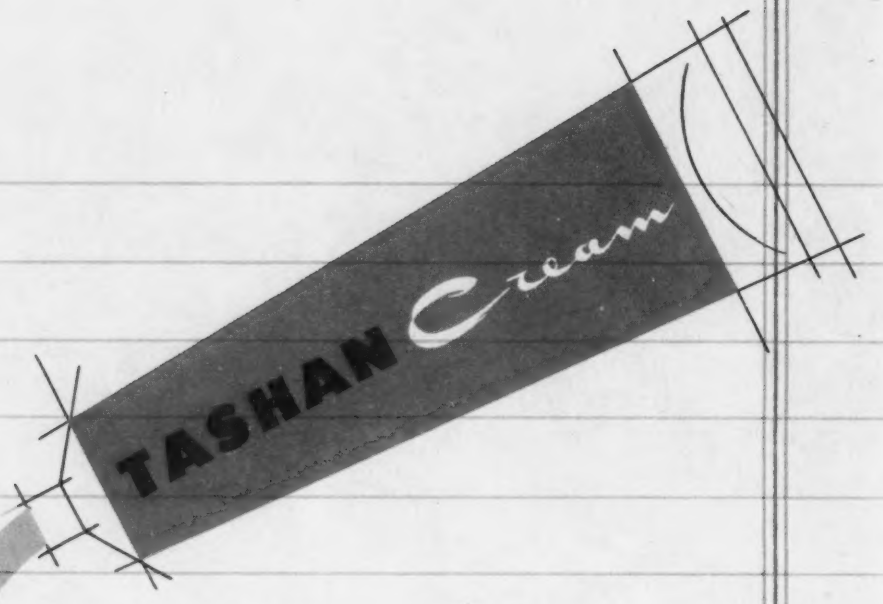

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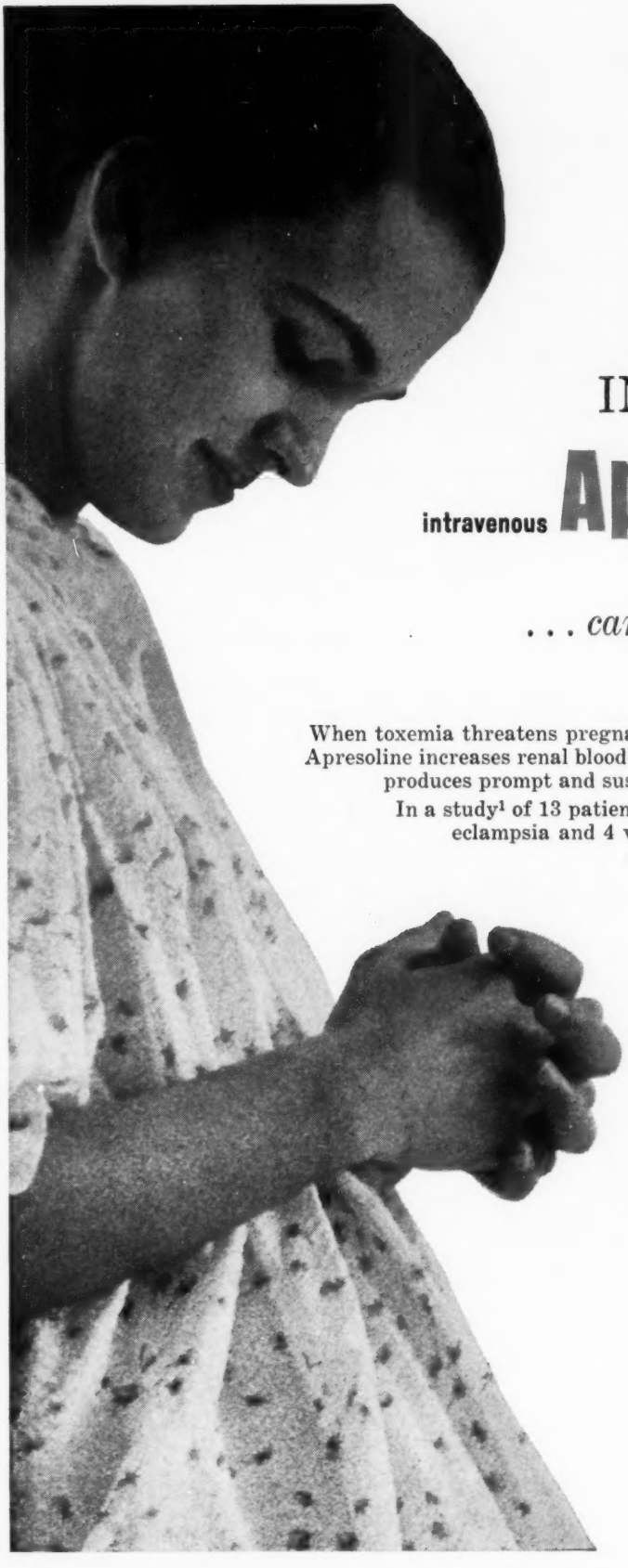

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When toxemia threatens pregnancy, Apresoline can be life-saving. Apresoline increases renal blood flow, decreases vascular resistance, produces prompt and sustained reduction of blood pressure.

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1. Kistner, R. W.: J. Obst. & Gynaec. Brit. Emp. *61*:463 (Aug.) 1954.

SUPPLIED: *Ampuls*, 1 ml., 20 mg. per ml. *Tablets*, 10 mg. (yellow, double-scored), 25 mg. (blue, coated), 50 mg. (pink, coated); bottles of 100, 500 and 1000; *Tablets*, 100 mg. (orange, coated); bottles of 100 and 1000.

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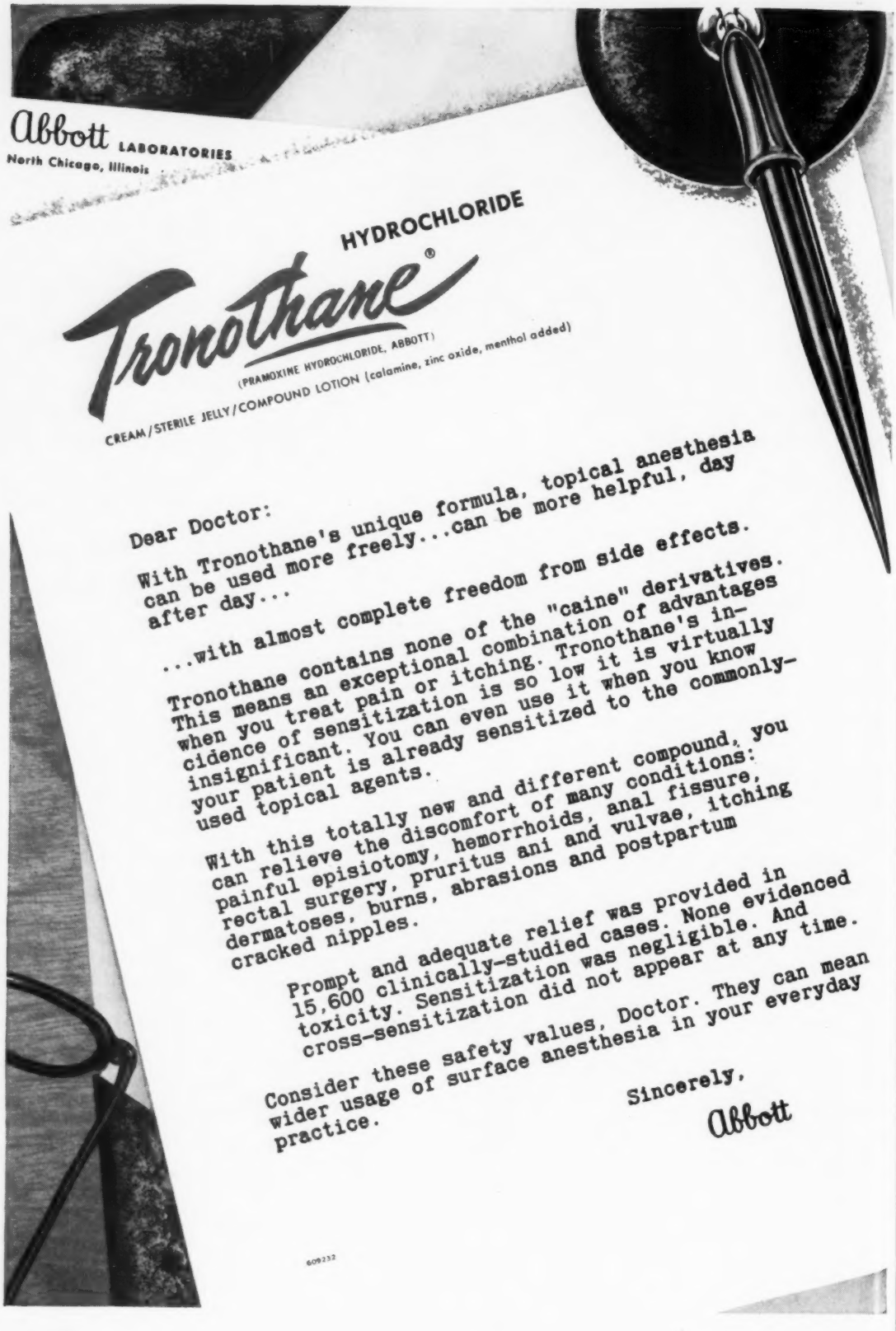

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3) *Quick and complete hemostasis at the line of circumcision.*

The Mogen Circumcision Instrument, clinically tested on more than 700 babies, assures complete, quick hemostasis at the line of circumcision. Its practical design and sturdy construction prevent side-slipping; beveled under edge and precision-engineered aperture prevents accidental injury to glans penis, while its flat surface assures accurate, clean excision of prepuce. The Mogen, made of stainless steel in a single unit, allows for precise gauging of prepuce and mucosa to be excised—the physician sees entire area of operation at all times. This same unit is adaptable for babies up to two years of age.

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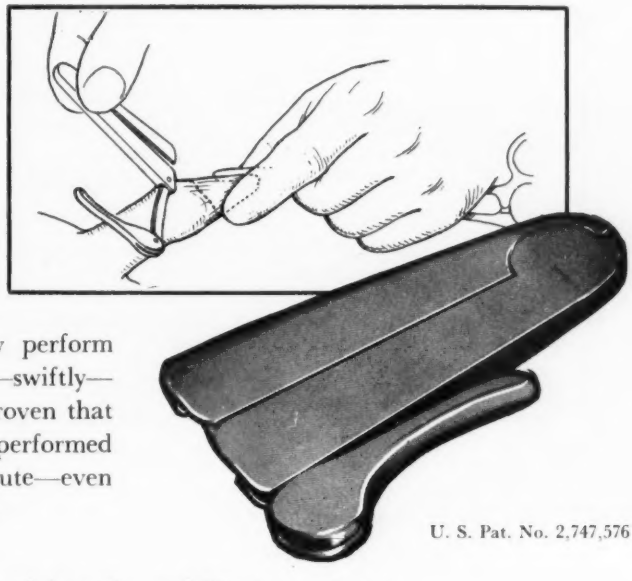

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For further information and literature write to:

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*Guest lecturer on circumcision in medical schools.

[1]Bleich, Alan A.: J.A.M.A. 143: 12, 1054 (July), 1950.
[2]Ewing, James: Quoted by Bessesen, D. H.: Med. J. & Rec. 135: 490, 1932.
[3]Dean, A. L.: as cited by McMann: Va. Med. Monthly 68: 216-218, 1941.
[4]Akl, Al F. M.: Amer. J. of Surgery 68: 402, June, 1945.

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References: (1) Hart, F. D., and MacLagan, N. F.: Brit. M. J. 1:512 (Mar. 4) 1950. (2) Starr, P., and Liebhold-Schueck, R.: J.A.M.A. 155:732 (June 19) 1954. (3) Starr, P.: Postgrad. Med. 17:73, 1955.

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[Iger, J., Kupperman, H. S.: Internat. Rec. Med. 168:723 (Nov.) 1955]

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Formula: in each vaginal tablet

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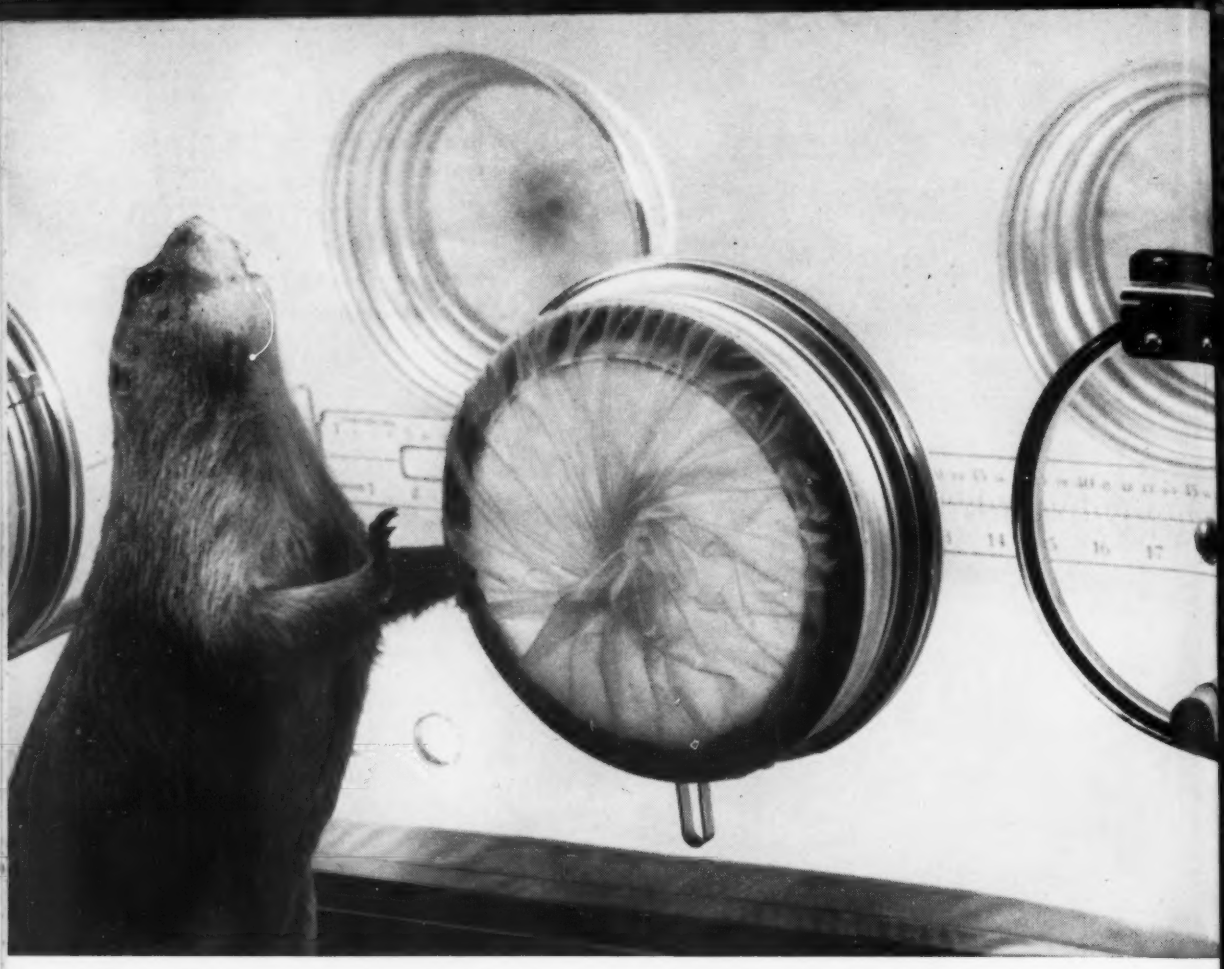

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Complete literature available on request.

References: 1. Hisaw, F. L.: Physiol. Zoöl. *2*:59 (Jan.) 1929. 2. Hisaw, F. L.; Meyer, R. K., and Fevold, H. L.: Proc. Soc. Exper. Biol. & Med. *27*:400 (Feb.) 1930. 3. Hisaw, F. L., and Zarrow, M. X.: Vitamins & Hormones *8*:151, 1951. 4. Perkoff, G. T., *et al.*: J. Clin. Endocrinol. & Metab. *14*:531 (May) 1954. 5. Abramson, D., and Reid, D. E.: J. Clin. Endocrinol. & Metab. *15*:206 (Jan.) 1955. 6. Eichner, E.; Waltner, C.; Goodman, M., and Post, S.: Am. J. Obst. & Gynec. *71*:1035 (May) 1956.

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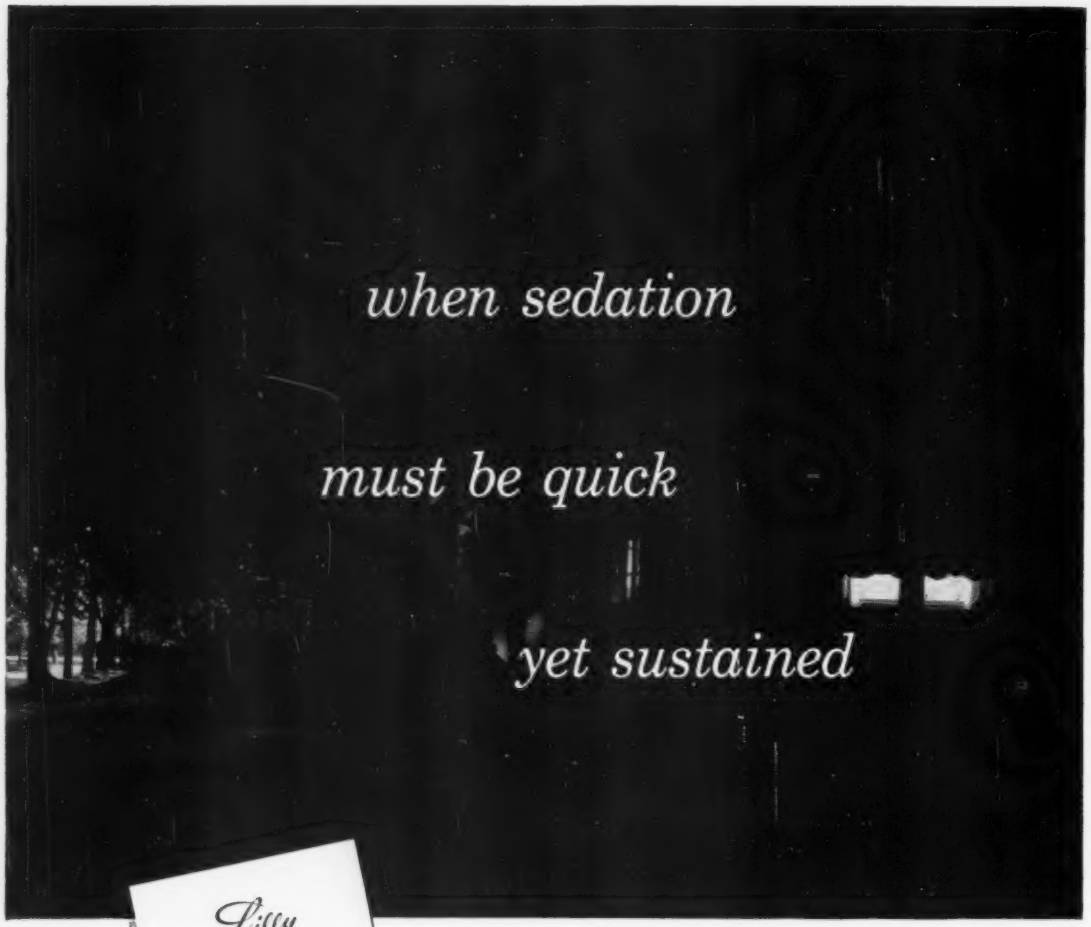

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CANCER OF THE CERVIX, AN APPRAISAL*

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(From the Vincent Memorial Hospital, the Pondville Hospital [Massachusetts Department of Public Health], and the Palmer Memorial Hospital)

WE ARE now trying to substitute intelligence for dogmatism in the treatment of cancer of the cervix, both radiation and surgical. The physician should understand both methods of treatment and, if not capable of accomplishing both himself, he should have on his team men capable of carrying out both methods. It is not intelligent to maintain that there is only one method of treatment for it is obvious from the results that both methods have cured patients for many years. I have lived through both the radiation and the surgical enthusiasm and am sure that both are good, but that selection of cases is the real advance of the last five years. If a patient is given radium and x-ray treatment and the treatment fails and then, after surgical treatment, she is cured, who can say that surgery cured her and that the radiation was of no use? It *may be* that the radiation treatment so conditioned the lymph nodes as to make the surgical extirpation successful. Who can say that after surgical treatment when a recurrence occurs in the vault of the vagina and radium destroys the lesion that the preliminary surgical treatment of the rest of the vagina, the parametrium, and the nodes did not aid enormously in the cure of the patient? It is not that I am becoming doubtful about the correct method of treatment of this disease and avoiding taking a definite stand; it is because after many years of observation of the disease and its treatment that I feel sure that some cases will do well with radiation

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and some with surgery and that our job is to find out before treatment which is the better method for the individual patient. In my opinion, and I trust I am observing and thoughtful, the combination of full radiation (x-ray and radium) treatment and radical surgery is a mistake and may be a very serious one. I have seen too many disasters from this method of approach to have any faith in it. Without doubt partial radiation and not too radical surgery may be safe and successful, but from my experience I would rather not use even that method. I believe one or the other should be the primary treatment.

This paper is written to give consideration to the various possibilities in the attack upon a cancer that can and should be curable in a high percentage of cases, at least 80 per cent in the early invasive cases, and between 40 and 50 per cent of all cases presenting. Surely with careful observation of the cervix and with care in obtaining smears and biopsies and with intelligence in treatment a new era should dawn in the treatment of the lesion—and if in this cancer, then why not in many others? It does not seem likely that cervical cancer is different, except in its location, from many other epithelial growths. Early diagnosis and proper treatment should aid in the cure of many of our serious malignant lesions.

Diagnosis

It is perhaps superfluous to go over with my audience the obvious methods of diagnosis but emphasis and re-emphasis are permissible, I feel sure. The history of course aids in the diagnosis and any change in discharge or bleeding from the vagina should be carefully investigated. A vaginal smear should be taken from the pool behind the cervix before any examination by finger or speculum is done. After the smear has been taken, the cervix can then be carefully palpated to note its position so that a speculum can be introduced without bruising the cervix. Then, with a speculum, without lubricant and with only water to moisten it, the cervix is gently brought into view. At this point observation with the colposcope is of great value, provided the user is familiar with the method. It is of no real value to use the instrument unless the operator has had definite training in the method and instruction from an expert. I believe that its value could be great, at least in making the observer conscious of the anatomy of the cervix at 10-20 times magnification. Perhaps few cancers will be actually diagnosed, but many abnormal types of epithelium will be observed and will become familiar to the colposcopist. I have never made the diagnosis of cancer of the cervix because I used the colposcope, but I have learned much about the anatomy of the cervix from the enlarged picture. After the colposcopic examination, the cervix should be painted with double-strength Schiller's solution, for in our hands ordinary Schiller's is too light. We use a solution of two parts of iodine, four parts of potassium iodide, and 300 parts of water. This solution does not burn the tissues and is dark enough to give good staining to the cervical epithelium. The Schiller test, like the colposcope, will not make the diagnosis of cancer of the cervix but it will point out areas of abnormal cervical epithelium that do not stain. These are the areas to be biopsied. After this has been done it is worth while to get a throat stick scraping of the cervix by the method suggested by Ayre.[1] This method disturbs the cervical epithelium so that subsequent biopsies may be interfered with as far as the histologic picture of early cancer is concerned. However, the use of this diagnostic tool is a decision the

individual examiner will have to make. After the scraping, or if the cervix has not been scraped, biopsies should be taken from the areas of nonstaining epithelium, at the junction of the stained and the unstained. It is my feeling that the biopsies should be taken at 12, 3, 6, and 9 o'clock, as nearly as possible, and that the tissues removed should be marked for reference so that the area from which the biopsy was obtained can be recognized after the pathologic report has been returned. Next, the endocervical canal should be curetted with a small, sharp curette, for the canal itself is often involved as a part of the ordinary lesion or as the primary area of involvement. If the smear is positive and no definite lesion can be seen, or if the biopsy is called cancer in situ, then the patient should be examined under anesthesia and a cone removed from the cervix, with a sharp knife and not an electric apparatus of any sort. The exact position of the tissue should be noted for future reference. If invasive cancer is found on biopsy then the proper treatment should be outlined. There can be no question concerning the value of the vaginal smear for by this means cancers that are invisible to the naked eye can be found. Routine biopsy will of course pick up about as many; but how many of us actually do routine biopsies? The combination of smear and biopsy greatly enhances the possibilities of early diagnosis and it is apparent from Navratil's[12] experience that the colposcope may aid in picking up an occasional lesion when the smear is negative. I doubt if it will often locate a tumor that the smear and biopsy have both failed to demonstrate.

Cancer in Situ

In the previous discussion cancer in situ was mentioned and a consideration of this disputed lesion follows. There is no doubt but that real true cancer in situ can be diagnosed histologically nearly 100 times out of 100. In cancer in situ the epithelium of the cervix has the same appearance as is seen in extensions along the top layer of the epithelium from invasive cervical cancer, the so-called "sugar-coating" of the Germans. In situ lesions have not penetrated the basement of the epithelium. The diagnosis is easy and clear but there are many variations and changes in the cervical epithelium that have been confused with cancer, including basal-cell overactivity, epidermidalization, and changes in the transitional and basal layers. It is doubtful that we are sufficiently accurate in our diagnosis of this condition. The study by 24 pathologists of Siegler's 20 histologic slides of changes in the cervical epithelium presented at the Meeting of the Inter-Society Cytology Council in Boston in November, 1954, demonstrated, in spite of all criticism of this method of testing, that there is *no* agreement among pathologists. It was obvious that the pathologists and gynecologists and their assistants could not agree on the diagnosis. This demonstration of Siegler's and a paper by Cole,[5] in which it was demonstrated that there was very little agreement in making the diagnosis of cancer of the stomach by the roentgenologist, surgeon, and pathologist, and the paper by Cochrane and Garland[4] in *Lancet*, 1952, demonstrating the variations in the diagnosis of chest conditions by different roentgenologists are of great interest, showing that in certain lesions the diagnosis is often difficult. Human error is very great and what one pathologist calls invasive cancer another will call cancer in situ, and in some cases will not even call cancer at all. This latter experience occurred to me not long ago on a trip to a Midwestern state. The tumor in question is in the records of a gynecologist as invasive cancer, but others of us on viewing the slide do not believe it to be cancer at all. This part of my discussion was stimulated by a recent visit to Dr. Walter Dannreuther, who says that his pathologist must be different from others or his material different for he

rarely sees a case of cancer in situ. For this reason it has seemed to me that the only accurate appraisal of the results of the treatment of cancer of the cervix would be to use only Stage II and Stage III cases and to eliminate from comparison Stage I and Stage IV. What the outcome will be to the cancer in situ question, it is not possible to state, but it seems to me to be a problem for the pathologists to settle. Could they not lay down definite criteria, or do they find it impossible to do so; and do they have the same difficulty in other tumors in other locations? It is much better to err on the side of radical treatment but some of the surgical and radiologic results are not too pleasant to contemplate. Further study and investigation should help this problem which is in such a state of confusion.

Treatment

The radiologic treatment of this disease is not so clear cut as could be wished, but it is obvious from a perusal of the *Annual Report on the Results of Treatment in Carcinoma of the Uterus,* tenth edition, that many clinics throughout the world are obtaining nearly the same results. The attitude of the radiologist should be to get a lethal dose into all tumor areas and their direct and lymphatic extensions without too severely injuring the normal tissues, especially important near-by organs. In our own clinic we found that we had many too many bladder and rectal injuries. To correct this therefore we started a search for a method that consistently produced good results with a low percentage of injury to the bladder and rectum. The better method was found in the Stockholm method and since 1949 we, in our hospital, have kept a very close liaison with Drs. Heyman, Kottmeier, Leissner, and Gorton. We feel that we now have a very satisfactory method of treatment and have decided to follow it as closely as possible. Recently, after a year's trial, our cancer of the cervix team (Drs. John B. Graham and Milford Schulz, who are carrying out our study of the proper treatment in "The Study of the Optimum Treatment of Cancer of the Uterine Cervix" for the Boston Hospitals and the American Cancer Society) returned to Sweden to consult about their failures. It was obvious to them that we were not quite up to their standards either in our radium applications or in our method of using our 1 and 2 million volt x-ray machines. We hope after this summer's consultation that the second year will bring fewer failures and that our treatment will be more like theirs. It has seemed to me, though not actually on the team but very much interested, that we can never completely adopt their methods but that we will eventually evolve a similar method with variations that will be satisfactory to us. It is possible that the Swedes who are a uniform race are different in their reaction to radiation from our native-born Americans and our Irish, English, Negroes, etc. I also believe it is possible that in those countries where the population is poorly nourished the results may be very different. All factors cannot be the same and what is good for one may not be good for others. Radiation can effect cures of cancer but it is also a very destructive and injurious weapon and its use deserves the greatest care and thought. The use of colloidal gold given into the parametrium, and the use of cobalt wire, as advocated by Allen[2] and Barnes,[3] respectively, are methods that are in the process of study and although one can see possible good it is also possible to visualize definite damage and injury. Let Drs. Allen and Barnes continue their studies and some day they may be able to tell us how valuable the methods are and how safe to use. Results are difficult to evaluate and in the past we have considered our own so poor that I have written of it and approved our search for better and safer methods. But now, since we have obtained a 100 per cent follow-up of our cases we have found them to be much

better than we realized—so good that for the eight years from 1942 to 1949 we have had 622 cases and have "cured" at five years 280, or 45 per cent. This relative cure figure for those eight years of true invasive cancer range from 40.3 per cent in 1942 to a cure rate of 49.4 per cent in 1944. These figures are certainly as satisfactory as most others so we must now ask ourselves, why seek a new method? Our poor results and our unhappiness with our method is because we reported "lost" patients as dead and because we all remembered the sad cases of fistulas, etc., from overtreatment. It is also true that in this series surgery was used in 22.1 per cent of the 622 cases. Some of the cases were surgical failures and were treated by radiation and some were surgical cures of radiation failures. It is difficult to evaluate the importance of surgery. This point will be further analyzed in a later part of the paper.

It appears that, on a percentage basis of cases reported by our hospitals in the *Annual Report*, of those treated by radiation in Stage I, 55.0 per cent of 104 patients lived without disease for five years and 74.0 per cent were cured by surgery. In Stage II, the differential narrows and 44.0 per cent of those radiated survived five years living and well, and 51.0 per cent were relieved by surgery. In Stages III and IV there was but one surgical case. It must be understood that this comparison is not fair as some of the surgical patients had radiation and most of the good-risk patients were in the surgical group. The differentials, however, in Stages I and II should be noted. The differentials certainly suggest that the surgical treatment is valuable (Table I).

TABLE I. 1942-1949

	STAGE I		STAGE II	
	NO.	%	NO.	%
Total cases	211		282	
Cured	136	64.4	127	45.0
Radiation	107		249	
Cured	59	55.0	110	44.1
Surgery	104		33	
Cured	77	74.0	17	51.0

The surgical treatment used in the Vincent Memorial Hospital and the Pondville Hospital (Massachusetts Department of Public Health) consists of a radical operation. It can be easily seen that our operation, as illustrated in the book, *Surgical Treatment of Cancer of the Cervix*,[15] is a definitely more radical operation than that of the late Dr. P. Werner of Vienna whose operation is as close to the Wertheim operation as he, a pupil of Wertheim, can make it. It is not so radical as that advocated by Dr. Brunschwig who advises removal of the internal iliac artery and vein in every case. This I feel sure is not necessary and in many hands would lead to disastrous hemorrhage. The Japanese operation advocated by the late Dr. Okabayashi is an excellent method. It is my feeling that the same amount of tissue is removed by our operation as by that one. The problem concerning the value of the removal of lymph nodes and the question of ureterovaginal fistulas from these operations will be discussed later. There is no doubt about the safety of the operation for the mortality is extremely small, there being no operative mortality in this series. The main objection to the surgical operation is fistula formation. The problem also arises as to whether in some instances removal of the nodes and interference with their channels may not be dangerous and open up a chance for rapid extension of the tumor.

Sensitization Response and Radiation Response

It is essential, considering our study of the disease, that a discussion be presented of the sensitization response or S.R. and the radiation reaction or R.R. These two responses have been noted and named as the result of experimental studies of Graham and Graham.[7-10] In the sensitization response changes are found in the benign basal cells, not in the cancer cells. The S.R. cells show dense, basophilic cytoplasm. The cytoplasm is dense and there is fine vacuolization of the cytoplasm. The radiation reaction is found in the nonmalignant cells of the vaginal epithelium. These changes consist of multiple nuclei, increase in size, cytoplasmic vacuolization, and nuclear changes.

In 1930 Drs. Joe V. Meigs and Frederic Parker[14] demonstrated that in certain instances during treatment with radium there was a complete disappearance of mitotic figures and that in others there was a great recrudescence of them four days after radiation treatment. It was shown that those with a flat curve lived and those with a recrudescence died. We believed that patients and their tumors acted differently to radium. This work was the start of my interest in the problem of radiation sensitivity and resistance.

For many years at the Pondville Hospital (Massachusetts Department of Public Health) we have been cognizant of the fact that there are patients who respond to radiation and those who do not. Warren,[16] the pathologist of that institution, and his associates decided that if after the radiation treatment a biopsy taken before discharge showed cancer with very little evidence of radiation change present the patient would succumb. Other patients whose biopsies demonstrated disappearance of the tumor and a good connective tissue response usually lived. This group of observations caused us to feel that there were inherent in tumors and in patients differences that prevented cure of all by means of radiation therapy. In addition it was a source of great distress to me to find that certain Stage I patients whom I felt I could cure by means of radiation returned in three months with disease still present. For these reasons I felt that modern surgery should be given a chance to see what it could do in the early cases. There is no doubt at all of the success of surgical treatment in many patients. If our idea of radiation response and resistance is correct then surgery must be good treatment, but surgical treatment fails in some cases, as does radiation. It was important to discover how we could best decide which patient should be operated upon and which radiated and how a selection could be made. It was at this point that Ruth Graham began to find evidence of radiation change in the normal cells in the vaginal smear. From her careful investigations she discovered that those patients with a good response in the normal vaginal cells to radiation were cured in a very much higher percentage than those showing no response. It was obvious that a way must be found to give a satisfactory test dose of x-ray or radium. If the result of the test dose showed a good radiation response radiation should be continued, but if a poor response resulted the patient should be assigned to surgery. It was during this investigation that she discovered benign basal cells whose cytoplasm was dense, finely vacuolated, and with a basophilic stain, which are the so-called S.R. cells, indicating a sensitization response. The sensitization response indicates a good response to radiation. Patients with a certain percentage of S.R. cells appeared to do well with radiation and to have a good radiation reaction or R.R. during treatment. Therefore, Graham and Graham felt that even before any radiation treatment was given they could select the patient to be radiated from the patient to be operated upon. These two phenomena, S.R. and R.R., are the bases of the study on selection being conducted in Boston in the Vincent Memorial Hospital, the Peter Bent Brigham Hospital, the Free Hospital for Women, and

the Pondville Hospital (Massachusetts Department of Public Health). This combined hospital study is under the leadership of Graham and Graham and the radiotherapeutist of the Massachusetts General Hospital, Schulz. We hope these studies and observations have placed us in a position of being able to treat cervical cancer intelligently. Glucksmann and Way[6] in England have tried using histologic slides rather than smears with the same idea. Others, notably Kjellgren[11] of Sweden and Nielsen[13] of Copenhagen, have confirmed the work of the Grahams. The surgical treatment of cancer of the cervix is now excellent and our Swedish method of radiation gives us good radiation therapy, so we are now in a position to give the selected patients good treatment.

Is the Surgical Treatment of Cancer of the Cervix Valuable?

It is difficult to demonstrate how valuable the surgical treatment is and the following is an attempt to do so. We feel that there can be no doubt of its value; but how can we prove it and how compare surgery with radiation? There should be no competition between the two methods of treatment for they are complementary. It is certain that both have value; but can we show that the surgical results have been worth the risk and occasional complication? If surgical treatment is valuable, what would have happened if operation had been done in cases that were failures after radiation treatment in a reported series? Would the cure rate have been higher? What would have happened if the surgical failures had been given radiation therapy? This actually is what our modern concept of treatment should be—well-trained surgeons to do radical surgery in those who *should* be operated upon and well-trained radiologists and gynecologists to give the treatment to patients who *should* have radiation. Only a series of cases, all treated by surgical means, none having radiation either before or after surgical treatment would give actual knowledge of the value of surgery. It is equally true that a radiation series would have to be treated by radiation only, with no surgical treatment for failures. Such a series will be difficult to obtain for certain patients of any clinic might conceivably go to some other clinic for treatment of their failures. For instance, a patient operated upon, who two years after operation had a recurrence in the apex of the vagina, might be treated by radium and remain free of disease at five years. This case should be called a radiation cure but the surgical treatment removed the lymphatics and nodes and this treatment may be largely responsible for the cure but radium helped relieve the local lesion and therefore the exact value of the treatments is in doubt. It is very difficult to determine which cured the patient in cases with combined treatment. It is my desire to make this report as fair as possible. Being one of the early advocates of surgery in the treatment of this disease after the nearly universal acceptance of radiation as the proper method I desire it be known that, although I am naturally very much interested in the surgical treatment, nevertheless I consider surgery in no way a rival of radiation but as a partner. In some instances it *should* be used and in others it should not.

The Material

In this paper the term five-year "cure" indicates patients living and well five years after treatment. It is acknowledged the word "cure" is not correct but it is simpler to use than survival and its meaning is well known. The material for this study consists of all cases, private and ward, in the Vincent Memorial Hospital, the Pondville Hospital (Massachusetts Department of Public Health) and the Palmer Memorial Hospital, operated upon by me.

Their histologic slides have been reviewed many times by our pathologists so that we all feel quite sure that no cancers in situ are included. I believe that some early invasive cases that are cured have been placed in the in situ category but I think it is unwise at this time to make any further change of grades. It appears that in our cases reported in the *Annual Report* surgery was helpful in Stage I especially and less so in Stage II. Some of these surgical cases were given preoperative or postoperative radiation or both, in the full amount, and others had only a part of the usual radiation treatment. On the whole in this study it appears that surgery played a large part in the cure, and the results make me feel that surgery is of great value.

The surgical cases presented and analyzed are in Stage I and II only. They were selected only in the sense that the patients who were considered poor operative risks were delegated to the radiologist for treatment. The surgeon is a good surgeon only if he is capable of selecting for his surgical operations those patients he thinks he is capable of operating upon safely. He would be a poor surgeon if he operated on patients who are not satisfactory risks when there is an alternate method of treatment. Selection for operation in this series is on the basis of operative risk and not on extent of disease. It is important to point out that there was no operative mortality. The selection for treatment by means of determining the sensitization response and radiation response will not be discussed in this group of patients as the method was not in use at that time.

Let us look at an analysis of these surgical cases done from 1940-1949 and see if we can come to any logical conclusion as we review the various bits of information. We know the number of patients who died of intercurrent disease but these are classified as dead of disease.

TABLE II. ANALYSIS OF SURGICAL CASES

CATEGORIES	NO. CASES	LIVING 5 YEARS	
		NO.	%
A. Surgery only	61	55	90.0
B. Surgery only (cancer at biopsy, no cancer at operation)	1	(Omitted)	
C. Surgery following radiation (radiation failures)	29	18	62.0
D. Surgery following radiation (no cancer at operation) (radiation cures)	20	19	95.0
E. Surgery followed by postoperative radiation (no preoperative radiation) (surgical failures)	10	3	30.0
F. Surgery following preoperative radiation (requiring postoperative radiation) (radiation and surgical failures)	10	1	10.0
Total	131	96	73.0

There are 131 cases in all (Table II); although one of the patients had invasive cancer at the original biopsy, no cancer was found histologically in the specimen removed at operation and although living and well we have decided to exclude her as her case is not pertinent to this study. If we take the patients who had surgery only, 55 of 61 (90.0 per cent) are living and well. In discussing the results of treatment we must call as failures those cases which had radium or x-ray treatment or both after a recurrence following surgical treatment. There were 3 out of 10 such cases which are now five-year cures. We have also excluded from the surgical cures those cases which were previously treated by radiation with recurrence and were subsequently treated by surgery and are now five-year cures. In estimating the results we take the patients who had no radiation

before or after their surgical operation and add to the number column but not to the cured column those whose tumor recurred after operation and who subsequently had radiation (categories *A* and *E*). There were in this group 71 patients with 55 successes, or 77.5 per cent five-year cures. Thus, we can give a figure for surgery alone. The patients were in Stages I and II and the figures demonstrate that in the group selected for surgery a very satisfactory cure rate was obtained. If we include the straight surgical patients, the surgical failures who had subsequent radiation, and the radiation failures who were operated upon (categories *A*, *C*, and *E*) there would be 100 patients and 76, or 76.0 per cent are living at five years. This sort of division of cases is difficult to follow but must be demonstrated. If we analyze those patients who had planned radiation in conjunction with surgery (categories *C*, *D*, and *F*) there are 59 patients of whom 64.4 per cent are living and well. It is obvious that the straight surgical cases, including the group with recurrence after radiation (*A* and *C*), had the best results—81.0 per cent. It can be seen here that the straight surgical cases with the surgical failures and cure by radiation, categories *A* and *E*, seem to fare second best; 77.5 per cent of five-year cures is a satisfactory result. Table III demonstrates these facts very well. The various categories are charted and given a letter, then the various categories can be placed together and various combinations studied. By dividing the straight surgical cases into Stages I and II (Table IV) the numbers are really small, and it is found that 40 of 45, or 89.0 per cent, of Stage I are living and well. Fifteen of 16, or 93.8 per cent in Stage II are without disease. The percentage of nodes in Stage I was 15.5 per cent and 3 of 7 patients are living at five years. In Stage II the percentage of nodes is 25, and 3 of 4 patients are well at five years. In Stage I there were 6, or 13.3 per cent, of ureterovaginal fistulas and in Stage II, 2, or 12.5 per cent.

TABLE III. COMBINATIONS OF CATEGORIES COMPARED

	CATEGORIES	NO. CASES	LIVING	
			NO.	%
Straight surgery and surgery with postoperative radiation	*A* and *E*	71	55	77.5
Surgery and surgery of radiation failures	*A* and *C*	90	73	81.0
Surgery and surgical and radiologic failures	*A*, *C*, and *E*	100	76	64.4
Radiation and surgery	*C*, *D*, and *F*	59	38	76.0

The method (used in Table III) of adding the categories together will be followed later when considering nodes, results, fistulas, and ten-year results.

It is very interesting to note the amounts of radiation given patients and the results obtained when combined with the surgical treatment, the surgical treatment being constant throughout the entire study (Table V).

The patients who had radiation in conjunction with surgery (*C*, *D*, and *F*) showed a 64.4 per cent curability and of 16 patients in this group with positive nodes 31.2 per cent survived. The results in patients with positive nodes will be compared in a table with the results in the other categories (Table VI).

The percentage of positive nodes is about the same in all categories, the incidence slightly higher in the radiated cases and yet the cure better by a modest per cent in the straight surgical group. No conclusions can be reached. Taking the cases together that had radiation preoperatively and with cancer at the time of operation (29) and those with preoperative radiation and no cancer found at operation (20), or 49 patients (categories *C* and *D*), 37 (75.5 per cent) are living and well; only 8 (16.3 per cent) had positive nodes and 4 of those (50 per cent) are living. Thus, this radiation group has the lowest incidence of nodes in this study with an excellent recovery for five years of

TABLE IV. CATEGORIES COMPARED IN STAGES

CATEGORY	NO. CASES			LIVING					
					NO.	%	NO.	%
A. Surgery only	Stage I 45 Stage II 16	61		Stage I Stage II	40 15	89.0 93.8	55	90.0
B. Surgery only (cancer at biopsy, no cancer at operation)	Stage I 1	1		(omitted)				
C. Surgery following radiation (radiation failures)	Stage I 18 Stage II 10 Stage III 1	29		Stage I Stage II Stage III	11 6 1	61.1 60.0 100.0	18	62.0
D. Surgery following radiation (no cancer at operation) (radiation cures)	Stage I 13 Stage II 7	20		Stage I Stage II	13 6	100.0 86.0	19	95.0
E. Surgery followed by postoperative radiation (no preoperative radiation) (surgical failures)	Stage I 5 Stage II 5	10		Stage I Stage II	3 0	60.0	3	30.0
F. Surgery following preoperative radiation (requiring postoperative radiation) (radiation and surgical failures)	Stage I 2 Stage II 8	10		Stage I Stage II	1 0	50.0	1	10.0
Total	Stage I 84 Stage II 46 Stage III 1	131		Stage I Stage II Stage III	68 27 1	81.0 58.7 100.0	96	73.0

TABLE V. AMOUNTS OF RADIATION GIVEN COMBINED WITH USUAL SURGICAL TREATMENT AND RESULTS OBTAINED

	NO. CASES	LIVING	POSITIVE NODES	
			NO. CASES	LIVING
¼ x-ray	1	0	1	0
½ x-ray	11	9	1	0
½ radium	9	8	0	0
½ radium, ½ x-ray	13	7	8	2
Full x-ray	7	5	2	1
Full radium	2	2	1	1
Full x-ray, ½ radium	3	2	1	1
½ x-ray, full radium	1	0	1	0
Full x-ray, full radium	12	5	1	0
Total	59	38(64.4%)	16	5(31.2%)

TABLE VI. NODES

CATEGORY	NO. CASES	POSITIVE NODES		LIVING	
		NO.	%	NO.	%
A	61	11	18.0	6	54.5
A and *C*	90	19	21.1	10	52.6
A and *E*	71	17	25.3	7	41.0
A, *C*, and *E*	100	25	25.0	11	44.0
C, *D*, and *F*	59	16	27.1	5	31.2

TABLE VII. FISTULAS

CATEGORY	NO. CASES	FISTULAS	
		NO.	%
A	61	8	13.1
A and *E*	71	10	14.1
A, *C*, and *E*	100	15	15.0
C, *D*, and *F*	59	5	8.4

4 of the 8 patients with positive nodes. Perhaps the radiation destroyed some nodes and yet in spite of the interference with lymphatic channels by surgery, which we think may be deleterious, those with nodes in this group did better than the usual run of patients with positive nodes. It is possible, but it is hard to prove, that radiation can destroy or perhaps isolate nodes in the pelvis. The low percentage in this group is otherwise difficult to explain.

It is important to analyze the incidence of ureteral fistulas in the various categories, as we have for the cures, nodes, etc. (Table VII.)

The number of fistulas in those patients who had radiation with or without cancer at the time of operation is lower than those in the more pure surgical groups.

I still have a definite fear of the combination of full radiation and surgical extirpation, but from my results it looks as though moderate radiation may be safe. My impression, however, if impressions are of any value to us, is to beware. I cannot advocate the combination. The cases in this series that received full radium and full x-ray treatment before their radical operation, although numbering but 12, show that only 6, or 50 per cent, have lived. This is not a satisfactory figure compared to the others. I have been most concerned about fistulas, but perhaps it would be best to worry about results. It is fully realized that the series is very small, but the trends are there.

Ten-Year Results

In considering the ten-year results the numbers are few but the consistent trend of results is satisfactory. The percentage of death due to intercurrent disease is 4.6 per cent in the five-year results and rises to 8 per cent in the ten-year results. This 8 per cent must definitely lower the figures for ten years. For what they are worth the ten-year results are as shown in Table VIII.

TABLE VIII. TEN-YEAR RESULTS

	NO.	%
No. cases	64	
Living	41	64.0
Positive nodes	14	21.9
Living (positive nodes)	4	28.6

Using the categories as presented in the five-year results, the ten-year findings are shown in Table IX.

TABLE IX. TEN-YEAR RESULTS ANALYZED BY CATEGORIES

		LIVING		POSITIVE NODES			
				NO. CASES		LIVING	
CATEGORY	NO. CASES	NO.	%	NO.	%	NO.	%
A	29	24	82.8	5	17.0	2	40.0
A and *E*	35	25	71.4	8	22.9	2	25.0
A, *C*, and *E*	47	31	66 0	11	23.0	4	36.0
C, *D*, and *F*	28	16	57 0	6	21.4	2	33.3

No sweeping conclusions can be made, but the straight surgical cases do as well as those combined with radiation. The 28 patients in the categories *C*, *D*, and *F*, the most radiated of the surgical cases, did not do quite so well as the others, but it is impossible to draw any conclusions. There appears to be a 10 per cent drop in the living and well column for the second five years in all but the straight surgical group.

Conclusions

1. The surgical results in this series are good.

2. The radiation as given in this group of surgical patients did not help statistically but did cure 3 of 10 surgical failures.

3. Patients who had planned preoperative radiation had the smallest percentage (16.3) of positive lymph nodes (*C* and *D*). Fifty per cent of these patients with positive nodes are living at five years, a creditable showing.

4. From a survey of the Vincent Memorial Hospital and the Pondville Hospital (Massachusetts Department of Public Health) results as tabulated for the *Annual Report*, it is obvious that surgery helped the total results. It must be remembered, however, that the patients operated upon were probably the best-risk patients and therefore it is possible that radiation might have done the same thing.

5. It is conceivable that surgery will cure radiation failures in a fair percentage of cases and that radiation will cure some of the surgical failures. Thus, this definitely leads us to the importance of selection and we may hope that the study of the sensitization response (S.R.) and radiation reaction (R.R.) will do it for us.

6. Fistula formation is too frequent, averaging from 8.4 to 15.0 per cent and pelvic radiation apparently has but little effect on its frequency in this series.

7. The cure of patients with positive nodes is excellent, running from 31 to 55 per cent in the five-year results to 25 to 40 per cent in the ten-year results. On the whole, the patients who have radiation seem to do about the same as the others in this group with none.

8. This study suggests that radiation and surgery are complementary and that results in the hands of experts will be good whichever method is used, but it does suggest the importance of selection.

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I. URINARY TRACT FISTULAS FOLLOWING RADICAL SURGICAL TREATMENT OF CARCINOMA OF THE CERVIX (EXCLUSIVE OF EXENTERATIONS)*

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THE radical surgical attack upon cancer of the cervix entails a risk of injury to the urinary tract. This is unavoidable by the very nature of the operations performed. It is our opinion that when the incidence of such complications is negligible in any significant series of patient, the operations carried out were not as extensive and thorough as they might be for cervical cancer. Whether relatively conservative operations with a lower incidence of urinary fistulas as complications will afford results in cancer control equal to the more radical procedures is a question to be answered in the future.

In the Gynecological Service of the Memorial Center for Cancer and Allied Diseases a surgical program has been instituted for the primary treatment of all cases of carcinoma of the cervix on the Gynecological Service since September, 1947. During the period September, 1947, to Dec. 31, 1950, 212 operations envisaging cure were performed for cancer of the cervix in Stages I, II, III, and IV. This number is exclusive of exenterations, but includes instances of recurrent carcinoma following radiation therapy with or without previous relatively conservative surgery. The Type IV cases in this series had segmental resections of bladder or ureter, or ligation of the latter above transection. Nineteen instances of carcinoma of the stump are included in the series. Selection of patients was minimal; rarely was a patient refused operation because of medical complications, obesity, or advanced age.

The individual records of these patients were reviewed in detail by one of us (H. C. F.) as concerns postoperative urinary fistulas and what subsequently happened to the patients. This group represents patients operated upon five or more years ago.

The operations varied to suit the situations encountered in each patient. The procedure envisaged was always a radical panhysterectomy with pelvic node dissection but not infrequently this extended procedure was regarded as too severe for the patient in question and, therefore, a less extensive procedure was done (Wertheim, or Schauta). The radical panhysterectomy and pelvic node excision have been previously described.[1] In the earlier periods of this surgical program the ureters were completely mobilized from the brim of the

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true pelvis to their entrance into the bladder. In the course of this phase of the operation they were rather closely stripped of periureteral connective tissue. No attempt was made to preserve ureteral arterial branches and all tissues in the lateral pelvic spaces including peritoneum were resected. At present the periureteral connective tissue is preserved, as is also the mesial leaf of peritoneum attached to the upper half of the pelvic segment of the ureter. In the earlier periods, and at present, the obliterated hypogastric arteries were not preserved.

The purpose of this report is to summarize the experience with the patients who developed postoperative fistulas in order to secure, if possible, information to serve in future orientation of this type of surgery.

TABLE I. TYPE OF OPERATION PRECEDING FISTULAS

TYPE OF OPERATION	NO. OF POSTOPERATIVE FISTULAS
Radical hysterectomy and pelvic node excision	35
Excision of stump and pelvic node excision	8
Excision of stump, partial cystectomy, and pelvic node excision	1
Radical hysterectomy, pelvic node excision, and partial cystectomy	3
Schauta (radical vaginal hysterectomy)	1
Excision of stump, pelvic node excision, and ligation of one ureter	1
Radical hysterectomy and pelvic node excision with nephrectomy	1
Total	50

TABLE II. TYPES OF FISTULAS

TYPE OF FISTULA	NUMBER
Vesicovaginal	14
Vesicovaginal plus obstruction of ureter	4
Ureterovaginal, unilateral	21
Ureterovaginal, bilateral	3
Ureterovaginal and cutaneous	2
Vesicovaginal and cutaneous	2
Rectovesicovaginal	3
Bilateral ureterovesicocutaneous	1
Total	50

During the period September, 1947, to Dec. 31, 1950, as previously stated, 212 operations, exenterations excluded, for cure of cancer of the cervix (19 were for carcinoma of the retained cervical stump) were carried out. There were 50 instances of postoperative fistulas, an over-all incidence of 23.5 per cent for all types of fistulas. Comparison of this figure with those in other series reported is not in order because of the radicality of our operations, the fact that this series includes patients with postradiation recurrences, etc. Table I is a correlation of the type of operation and postoperative fistulas. Among the 50 patients with fistulas there were a number who had previously received some form of radiation and in the surgical specimens of this group there were 4 instances where routine pathological study failed to reveal residual cancer. Table II summarizes the incidence of the various types of fistulas that were encountered. All fistulas were the result of ureteral or bladder injury at operation that was repaired and subsequently broke down, or fistulas that developed after operation as a result of ischemia. In Table III a correlation is presented between the extent of the cervical lesion and the incidence of fistulas. Most of the fistulas were in patients whose disease had extended be-

yond the cervix. There were 18 instances in patients with disease limited to the cervix, and 32 where the carcinoma had extended beyond the cervix, i.e., almost double the incidence where the disease was limited to the cervix.

TABLE III. EXTENT OF DISEASE* AND NUMBER OF PATIENTS WITH FISTULAS

Disease limited to cervix†	18
Disease extended to vaginal fornices	11
Invasion of parametrium	8
Peripheral pelvic node metastases	7
Bladder and/or ureter invaded (segmental resection)	6
Total	50

*Verified histologically.

†Four of these had carcinoma of the cervix treated elsewhere by radiation and the surgical specimen did not reveal residual carcinoma on routine pathological study.

Among the 50 patients with postoperative urinary fistulas, 22 survived five or more years and are free of evidence of active cancer—a five-year survival rate of 44 per cent (over-all figure including cases in Stages I, II, III, and IV).

Ureterovaginal Fistula (Unilateral).—

Among the 21 instances, 9 resulted from accidental division of the ureter at operation with immediate repair over catheter (Table IV). All of these immediate repairs subsequently broke down, and this is attributed by us to the fact that the ureters had been trimmed rather closely during the operation and that there had been a radical excision of pelvic peritoneum and connective tissues. Repair of a divided ureter in a pelvis that has not been "skeletonized" presents a different situation from repair in a pelvis where a radical panhysterectomy and pelvic node excision have just been performed.

TABLE IV. OUTCOME IN 9 PATIENTS WITH URETEROVAGINAL FISTULAS RESULTING FROM FAILURE OF IMMEDIATE REPAIR OF ACCIDENTALLY DIVIDED URETER AT OPERATION

NO. PATIENTS	OPERATION	OPERATION FOR REPAIR	RESULT
4	Radical hysterectomy (or excision of stump) and pelvic node dissection. Accidental division of ureter	Immediate repair of ureter over catheter. Subsequent breakdown	Died of recurrence of cancer. In 6, 15, 22, and 37 months, fistulas remained unhealed
3	Radical hysterectomy (or excision of stump) and pelvic node dissection. Accidental division of ureter	Subsequent nephrectomy	2 died of recurrences 1 living and well 5 years
1	Radical hysterectomy (or excision of stump) and pelvic node dissection. Accidental division of ureter	Spontaneous closure, then slight leakage (until present)	Living and well 7 years
1	Radical hysterectomy (or excision of stump) and pelvic node dissection. Accidental division of ureter	Nephrostomy and reimplantation of ureter into bladder	Living and well over 5 years

There were 12 instances of ischemic postoperative ureterovaginal fistula, i.e., postoperative fistula where at the time of operation the ureters appeared uninjured. These are summarized in Table V.

Ureterovaginal Fistulas (Bilateral).—

Three other patients developed bilateral ureterovaginal fistulas on the basis of ischemia; 2 are living and free from disease over five years; one died of recurrences. One of the living patients developed her fistulas a month after

operation and had nephrostomies three months later; three years later she had bilateral ureterocolostomies that subsequently stenosed and these were then converted to cutaneous ureterostomies (permanent). The second living patient developed fistulas two months after operation, bilateral nephrostomies were done sixteen months later. Five years after the hysterectomy and node excision a right ureterosigmoidostomy was done and she is living and well six years after the original operation, with one nephrostomy. The third patient died of recurrences seven months after the original operation.

TABLE V. OUTCOME IN 12 PATIENTS WITH ISCHEMIC URETEROVAGINAL FISTULAS

NO. OF PATIENTS	OPERATION	OPERATION FOR REPAIR	RESULT
2	Radical hysterectomy and node dissection	None. Fistulas persisted	Died of recurrences 19 months and 3 years, respectively
2	Radical hysterectomy and node dissection	Ureterocolostomies (one bilateral)	Fistulas obliterated but died of recurrences 2 and 4 years, respectively
1	Radical hysterectomy and node dissection	Nephrectomy 6 months after original operation. Fistula cured	Died of recurrences 3 years
1	Radical hysterectomy and node dissection	Small fistula spontaneously healed	Died of recurrences 4 years
1	Radical hysterectomy and node dissection	Unsuccessful reimplantation of ureter into colon, then nephrectomy 14 months after original operation	Died of congestive heart failure (?), recurrence (?) 21 months after original operation
1	Schauta radical vaginal hysterectomy	Reimplantation of ureter into bladder. Leakage	Died of sepsis 1 month following repair
1	Radical hysterectomy and node dissection	None	Paraplegic, previous poliomyelitis. Adjusted to fistula, does not want repair. Well over 7 years
1	Radical hysterectomy and node dissection	Left ureterosigmoidostomy	Well over 6 years
1	Radical hysterectomy and node dissection	Left ureterosigmoidostomy after several attempts to heal over catheter	Well over 5 years
1	Radical hysterectomy and node dissection	Left nephrectomy, elsewhere 4 months after original operation	Well over 5 years

One other patient received radical panhysterectomy and pelvic node excision for postradiation recurrence extending to the vaginal vault. She developed bilateral ureterovaginal fistulas and vesicovaginal fistula fifteen days after operation. Bilateral nephrostomies were performed. She is living and well and in excellent general health six years after the original operation. The fistulas are closed but the nephrostomies are still functioning. The patient has made a very good adjustment to her nephrostomies and is normally active.

Vesicovaginal Fistulas.—

There were a total of 14 patients in this group. All received continuous urethral catheter drainage as soon as the diagnosis of vesicovaginal fistula was made.

In 4 patients the fistulas did not heal on this drainage and the patients died of recurrences five, six (two patients), and nineteen months, respectively, after the original operation.

In 2 patients the fistulas healed during the month after operation, but the patients died of recurrences an average of seventeen months after operation.

One patient underwent successful transvesical and transvaginal repair seven months after the original operation, but died in three years of recurrences.

Five patients are living and well over five years following spontaneous closure of the fistulas on catheter drainage. Two of them are incontinent due to sphincter and bladder atony (ascribed to the operation itself) and 3 have no urinary symptoms and have normal intravenous pyelograms. One of the well patients whose fistula healed on catheter drainage also had received a left ureterocolostomy for accidentally divided ureter at the time of the original operation.

There are 2 patients living and free from disease over six years following their original operation who received surgical repair of their fistulas six and eight months, respectively, after their original operations. One of them also received reimplantation of one ureter into the bladder.

In the other patient, the repair later broke down and two subsequent repairs were not entirely successful. There is a persistent small vesicovaginal fistula.

These cases are summarized in Table VI.

TABLE VI. OUTCOME IN FOURTEEN PATIENTS WITH VESICOVAGINAL FISTULAS FIVE OR MORE YEARS AFTER THE ORIGINAL OPERATION

NO. OF PATIENTS	OPERATION	OPERATION FOR REPAIR	RESULT
4	2 radical hysterectomy and pelvic node excision 1 stump and node excision 1 radical hysterectomy, excision of pelvic nodes,	No reparative operations Catheter drainage only	Died of recurrences 5, 6, 6, and 19 months, respectively. Fistulas did not heal
2	Radical hysterectomy and pelvic node excision	Catheter drainage only	Died of recurrences. Average survival, 17 months
1	Radical hysterectomy and pelvic node excision	Successful transvaginal and transvesical repair 7 weeks later	Died of recurrences 3 years after original operation
5	Radical hysterectomy and pelvic node excision	Catheter drainage only	Three living at least 5 years and fistulas healed. Two are living and without evidence of cancer with fistulas healed, but have vesicle incontinence
1	Radical hysterectomy and pelvic node excision	Three unsuccessful attempts at repair	No evidence of cancer, but has small vesicovaginal fistula
1	Radical hysterectomy and pelvic node excision	Successful closure after two attempts	No evidence of recurrence, but is incontinent

Vesicovaginal Fistula With Ureteral Obstruction.—

Four patients comprised this group: 3 are dead and one is surviving over six years after the original operation. One death was due to operation (from attack upon the fistula) on the fourth postoperative day following nephrectomy. Bilateral nephrostomies had been done one month after the original

operation and the right nephrectomy seven months later. The second patient received a right nephrostomy two months after radical hysterectomy and pelvic node dissection for carcinoma of the cervix that recurred two years after radiation therapy. She died of recurrent disease and had an unhealed fistula a year after the radical hysterectomy. The third who died had an unsuccessful attempt at vaginal repair one month after operation and died of recurrences twelve months later with an unhealed fistula.

The single survivor had unsuccessful transvesical repair with reimplantation of the obstructed ureter seven months after the original operation. A second repair via the vagina with removal of ten bladder calculi was likewise unsuccessful. Later the fistula healed spontaneously, but the patient is incontinent. She remains free from disease over six years after the original operation.

Closure of vesicovaginal fistulas, as in the case of ureterovaginal fistulas, presents a problem after radical panhysterectomy and pelvic node excision that is not comparable to that of obstetrical vesicovaginal fistulas, or fistulas occurring after simple hysterectomy or vaginoperineorrhaphy. In the former the skeletonizing of the pelvis, with consequent reduction in vascularity when the hypogastric arteries are resected, tends to reduce the likelihood of spontaneous healing.

Complex Lower Urinary Tract Fistulas.—

Vesicorectovaginal fistulas: There were 3 patients in this group. One had lymphogranuloma invading the rectum and bladder as a complicating feature. She underwent seven attempts at repair of the fistulas in another hospital subsequent to radical excision of the cervical stump and pelvic node dissection. For a time these fistulas remained closed. She eventually returned to this hospital, had skin ureterostomies because of repeated attacks of acute pyelitis. A rectovaginal fistula developed and a transverse colostomy was performed. Her general condition deteriorated progressively and she died in extreme cachexia without definite evidence for a specific cause of death (anorexia nervosa?). Necropsy was not obtained but during the last operations (cutaneous ureterostomies and transverse colostomy) no evidence of cancer was apparent. She survived seven years following the radical hysterectomy and pelvic node excision.

The second patient received radical excision of a carcinomatous stump, a segmental resection of the bladder, and implantation of the left ureter into the sigmoid. Three weeks later a vesicovaginal and rectovaginal fistula occurred. Recurrences developed and anterior pelvic exenteration was performed. Thirteen months later she died of recurrences.

The third patient had a radical hysterectomy and pelvic node dissection after intense radiation given elsewhere. Twenty days later rectovaginal and vesicovaginal fistulas developed. Three months later a loop transverse colostomy was made and four months after that, bilateral cutaneous ureterostomies. At present, five years after the original operation, she has no evidence of cancer and has a small perineal fistula draining a small amount of purulent material at intervals. She is fairly active.

Ureterovaginal and cutaneous fistulas: Two patients were in this group, both living without disease six years after their original operations.

One developed a right ureterovaginal and cutaneous (through the operative wound) fistula on the thirteenth day. Five months later a right nephrostomy was done elsewhere and a year and seven months later a right nephrectomy was carried out for persistent fistula. She is living and well over five years after the radical hysterectomy and pelvic node excision.

The second patient had a radical excision of the cervical stump and pelvic node excision. Two weeks later she developed a left ureterocutaneous and

right ureterovaginal fistula. The left ureteral fistula healed over a catheter in three weeks. The right ureter was re-implanted into the bladder two months after operation. Three months post operation she developed a fistula between the left ureter and left common iliac artery. This was an acute emergency and necessitated ligation of the left common iliac artery. The left ureter was implanted into the bladder. Four years later a radical gastrectomy was done for peptic ulcer by one of us (A. B.) and no evidence of recurrent cancer was observed in the abdomen at this time. She is well and without symptoms of cancer over six years after the original operation.

Vesicovaginal and cutaneous fistulas: There were 2 patients in this group. One received a radical hysterectomy and pelvic node excision with segmental resection of the bladder and right ureterosigmoidostomy. The vesicovaginal and cutaneous fistulas healed on catheter drainage in four months, but the patient died thirteen months after operation of recurrent cancer.

The second patient had a radical excision of the cervical stump and node dissection. The fistulas healed in three weeks and she is living and well over five years.

TABLE VII. STATUS OF "UROLOGICAL CRIPPLES" FIVE OR MORE YEARS AFTER ORIGINAL OPERATION WITH NO EVIDENCE OF RECURRENT CANCER

NO. PATIENTS	FISTULA	REPAIR	GENERAL CONDITION	URINARY TRACT
2	Vesicovaginal	Spontaneous closure, catheter drainage	Good	Vesical atony and incontinent
1	Ureterovaginal	Spontaneous closure for 2 years. Drainage renewed and persists	Good	Persistent ureterovaginal leakage. Did not desire repair. Lost to follow-up over five years after original operation
1	Ureterovaginal	None	Excellent	Right ureterovaginal fistula. Patient had poliomyelitis, is a well-adjusted paraplegic
1	Vesicoureterovaginal	Vaginal repair and ureter reimplanted into bladder	Excellent	No fistulas. Incontinent. Fully active
1	Ureterovaginal	Cutaneous ureterostomy	Good	
1	Vesicorectovaginal	Colostomy and bilateral cutaneous ureterostomies finally performed after multiple attempts at repair elsewhere	Fair—becoming poor. Invalid during last 2 years of survival period	Died in cachexia 7 years after original operation. No recurrence. Cause of death?
1	Bilateral ureterovaginal	Bilateral nephrostomies	Excellent	Bilateral cutaneous ureterostomies
1	Bilateral ureterovaginal	Ureterocolostomy and bilateral nephrostomies	Good	Left nephrostomy and right ureterocolostomy
1	Bilateral ureterovaginal and vesicovaginal	Bilateral nephrostomies	Excellent	Bilateral nephrostomies
1	Vesicovaginal	Transvaginal repair	Good	Recurrence of fistula with small leakage of urine from vagina

"Urological Cripples."—

"Urological cripples" are arbitrarily defined as those who wear one or two nephrostomy tubes, have cutaneous ureterostomies, are incontinent due to failure of urethral sphincter function, or who have persistent fistulas. This does not mean that their general condition is poor; quite the contrary, in the patients in this series it is satisfactory and most have returned to normal or near-normal activity.

Among 22 survivors for five or more years, 11 are practically normal individuals. Eleven may be classified as urological cripples and these cases are summarized in Table VII.

None of the urological cripples except one are bedfast, chairfast, or are appreciably curtailed in their general activities. The one patient died in cachexia seven years after the original operation and no evidence of cancer was clinically present. Table VIII summarizes the status of the patients without persistent urinary fistulas or dysfunctions.

TABLE VIII. DATA ON ELEVEN PATIENTS LIVING AND WELL AT 5 YEARS SINCE RADICAL SURGICAL ATTACK UPON CANCER OF THE CERVIX WHOSE POSTOPERATIVE COURSE WAS COMPLICATED BY URINARY TRACT FISTULAS. NO "OSTOMIES" AND FISTULAS CLOSED

PATIENT	FISTULA	METHOD OF REPAIR	RESULT
Ros.	Ureterovaginal	Nephrostomy and reimplantation of ureter into bladder	Fistula healed
Sol.	Ureterovaginal	Unsuccessful anastomosis, then nephrectomy	Well healed
Gerin.	Ureterovaginal	Ureterosigmoidostomies	Well healed
Har.	Ureterovaginal	Nephrectomy	Well healed
Garif.	Ureterovaginal and cutaneous	Nephrectomy	Well healed
Low.	Ureterovaginal	Reimplantation—bladder	Well healed
Mil.	Vesicovaginal and cutaneous	Healed with catheter drainage	Well healed
Ven. Owe. Fe.	Vesicovaginal	Catheter drainage	Well healed
El.	Vesicovaginal	Transvaginal repair	Well healed

Comment

Postoperative urinary tract fistulas following extensive surgical attack upon cancer of the cervix develop as a result of a variety of conditions and no two patients resemble each other. A consideration of the experience here recorded affords certain impressions:

1. In accidental division of the ureter within the skeletonized pelvis, end-to-end suture over a catheter has little chance of healing and in most instances the division will subsequently recur, producing a second fistula. It appears that reimplantation into the bladder, if possible, is the treatment of choice. If this is not feasible, ureterocolostomy or cutaneous ureterostomy would be indicated. Ligation of the ureter is to be considered as a possibility only if the operation has to be terminated rapidly. Some operators may prefer to ligate the divided ureter, but this entails the sacrifice of one kidney.

2. Ureterovaginal fistulas occurring postoperatively on the basis of ischemia may be observed for a period of six months at least to afford oppor-

tunity for spontaneous closure as this occurs sometimes, but not in the majority of cases. In this series, in a total of 21 patients, spontaneous closure occurred only once, and this fistula spontaneously reopened (partially) after two years. The extensive excision of soft tissue carried out at the original operation does not create a situation favoring spontaneous closure, quite the contrary. It appears that in such fistulas a period of several months should be permitted to elapse in order to favor subsidence of edema and then reimplantation into the bladder, ureterocolostomy, or nephrectomy may be performed or, under certain circumstances, the ureter may be ligated above the fistula. Certainly nephrectomy is the surest way to do away with a ureteral fistula, but its disadvantages are obvious. In such instances the choice of procedure is a highly individualized one.

3. In vesicovaginal fistula, catheter drainage should be instituted as soon as the diagnosis is made. Under expectant treatment the fistulas may heal spontaneously. There is greater chance for vesicovaginal fistulas to heal spontaneously with catheter drainage than there is for ureteral fistulas. When it becomes apparent after several months that spontaneous closure will not ensue, operative repair by one of a variety of methods is indicated.

More detailed suggestions for the management of these fistulas are not set forth because of the varying circumstances in each patient. Each instance is a problem unto itself. No hard-and-fast rules are possible to avoid these complications. Protection of the ureter will entail sparing the radicality of the operation for cancer of the cervix. The operator must balance one of these factors against the other.

4. In this series of patients with fistulas, some had received preoperative radiation therapy, others had recurrences following radiation, and a number had no previous treatment. Among the 50 cases of fistula, 9 were due to breakdown of a repaired ureter accidentally transected at the original operation. If these 9 are excluded, there remain 41 cases. In 20 of these radiation in some form had been given prior to operation and in 21 no radiation had been given. This limited series indicates that radiation received prior to operation did not contribute to the postoperative fistulas on the basis of ischemia. This is contrary to a widely held view that previous radiation tends to increase the likelihood of urinary fistulas if operation is then carried out. It may not be stated, however, that this view is controverted by the above fact in view of the limited number of patients in this series.

Summary

In the performance of radical surgery for cancer of the cervix (exclusive of exenterations), as previously stated, the occurrence of lower urinary tract injury is a hazard that must be expected and accepted. Avoidance of such complications, however, must be constantly kept in mind, and conservatism of the operative attack to obviate urinary tract damage must always be balanced against maintaining radicality in the attack upon cancer.

An actual experience based upon 212 consecutive operations envisaging cure of cancer of the cervix (excluding exenterations) is reported. The in-

cidence in this series of postoperative urinary tract fistulas was 23.5 per cent (50 instances). There were 27 ureteral fistulas, an incidencé of 12 per cent, and 23 vesical fistulas, an incidence of 11 per cent. There were two deaths attributable to the reparative surgery; an incidence of 4.3 per cent surgical mortality compared with about 1 per cent mortality for the cancer operation itself. Twenty-two of the patients who developed postoperative urinary tract fistulas were living and well, free from cancer five or more years after their original operation (44 per cent five-year survivals among all patients in Stages I, II, III, IV). Of the 28 patients who did not survive, 25 died of cancer in less than five years. Of the 22 patients who survived five years, 11 are classified as "urological cripples" because they have nephrostomies, cutaneous ureterostomies, persistent fistulas, or severe incontinence without "ostomies." These, however, all seem to be adjusted to their situations and are not invalided (except one). Eleven are living and well without fistulas or incontinence.

Since this series has been accumulated the radicality of the panhysterectomy and node dissection has been modified to preserve the periureteral layer of connective tissue and often the mesial leaf of peritoneum attached to the upper two-thirds of the pelvic portion of the ureter. These measures seem to have reduced the incidence of ureteral fistulas, but definite conclusions must await actual tabulations at a later date. This report as presented is intended as a record of experience to serve those who may embark on the surgical treatment of cancer of the cervix and to emphasize the hazard of closely stripping the ureters. Reports recently published of cases in which the dosage of radiation has been increased indicate an incidence of urinary tract fistulas appreciably above that often previously reported for complications of radiation therapy.

It is our opinion that while lower urinary tract fistulas are complications encountered in the radical surgical treatment of cancer of the cervix, they do not pose a serious deterrent to such treatment. The problem of urinary fistulas is one that can be coped with. In the development of the modern surgical attack upon cancer of the cervix, it behooves the original operator to become familiar with the fistula problem and while calling upon his urological colleagues for help and advice he should, as time goes on, perfect himself in the reparative surgery necessary and from his own experience develop judgment for the management of these and all other complications which may ensue from the original surgery.

We wish to thank Drs. Willet F. Whitmore and Victor Marshall of the Urological Service of the Memorial Hospital for their cooperation in the earlier portion of these studies, and at all other times when we have called upon them for advice.

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PELVIC EXENTERATIONS FOR ADVANCED CARCINOMA OF THE VULVA*

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CARCINOMA of the vulva occurs more frequently in the advanced age groups than in relatively young subjects, although in the latter it is not unusually rare. These neoplasms arise in skin and mucosa that have already undergone definite alteration (kraurosis, leukoplakia, etc.).

When the disease has encroached upon the urethra, the floor of the bladder (anterior vaginal wall), and the anus, a total pelvic exenteration is necessary to encompass the disease and afford an opportunity for palliation—and even prolonged survival. If the disease involves the vulva, urethra, and anterior vaginal wall (base of the bladder), an anterior exenteration may suffice. If the posterior vulva, vaginal wall, anal and perianal regions are involved, a posterior exenteration may be indicated.

The purpose of this report is to record an experience with the exenteration operations in 27 patients with advanced vulvar cancer in whom a type of exenteration operation was carried out.

The only contraindication to operation was clinical evidence that the disease had already spread beyond the contemplated area of operation. This series is entirely based upon *unselected cases.*

The techniques for anterior and total pelvic exenterations have been previously described[1] and were followed in this group of patients.

Anterior Pelvic Exenteration

There were 16 patients in this group. Their ages varied between 45 years and 75 years, with an average of 59 years. Seven were previously untreated, 3 had received conservative surgery only, one radiation therapy only, and 5 had received both radiation and surgery. The cases are summarized in Table I.

In 3 instances disease had apparently encroached upon the periosteum of the pubic arch to such an extent that resection of portions of the pubic rami were carried out by means of a chisel and hammer.

The mortality was high. In accordance with our general rule in reporting surgical mortality as death within thirty days of operation, this was a follows:

Immediately after operation, cardiac failure (Case 16)	1
Few hours after operation, hemorrhage (Case 4)	1
Shock on second day (Case 11)	1
Coronary occlusion on fourth day (Case 14)	1
Exhaustion on fourth day (Case 15)	1
Sepsis and uremia on sixth day (Case 1)	1
Sepsis on seventeenth day (Case 3)	1
Total	7 patients

*This report was facilitated by a grant to the Memorial Center by Mr. James Adams of New York City.

TABLE I. CARCINOMA OF THE VULVA TREATED BY ANTERIOR PELVIC EXENTERATION

PATIENT, AGE	PREVIOUS SURGERY	PREVIOUS RADIATION	DATE OF OPERATION	GROIN DISSECTION	INGUINAL NODES	SUBSEQUENT COURSE
1. Tir. 63 years	Yes	Yes	11/21/47	Previously	Positive	Died on sixth day, of uremia, acute necrotizing papillitis, sepsis
2. Zasl. 62 years	No	No	3/11/48	6 months after operation	Positive	Lived for 2 years, 5 months. Died of recurrences
3. Samd. 58 years	No	Yes	3/26/48	Yes	Negative	Died on seventeenth day; sepsis, pyelitis
4. Spin. 46 years	Yes	Yes	12/30/48 Bilateral ureterosigmoidostomy 1/6/49 Bilateral nephrostomies 1/27/49 Anterior exenteration	Previously	?	Died few hours after final operation of hemorrhage
5. Suth. 45 years	Yes (12 and 7 years previously)	Yes	9/29/49	Yes	Negative	Died of recurrences in 7 months
6. Rye. 66 years	No	No	10/25/49 Portion of pubic arch resected	Yes	Positive	Lived for 14 months and died in cachexia. No recurrent cancer. Received one laparotomy for intestinal obstruction
7. Dayt. 67 years	Yes	No	1/20/50	Yes	Positive	Small bowel fistula on tenth day postoperatively; attempted closure failed. Died in hospital 2½ months after original operation
8. Bersich. 75 years	Yes	Yes	2/28/50	No	—	Acute pyelitis on twenty-eighth day. After discharge from hospital sustained fractured hip and then "wasted away" and died 3 months after original operation
9. Synd. 62 years	No	No	6/16/50 Suprapubic cystostomy 7/11/50 Vulvectomy 7/20/50 Anterior exenteration	No	—	Urinary and colonic fistulas (each at site of ureterointestinal anastomosis). Transverse colostomy. Died in another hospital 11 months after original operation. No details of situation just prior to death are available

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10. Rosk. 67 years	No	No	12/1/50 Portion of pubic arch resected	Yes	Negative	Thrombophlebitis; cerebral accident. Died 3 months and 3 weeks after operation. Necropsy showed no residual neoplasm, but massive thrombosis in both iliac veins. There were other multiple large venous thromboses
11. Zim. 41 years	No	No	8/22/50	No	Clinically positive	Acute tachycardia on second day after operation. Died suddenly on third day. Massive hemorrhage from hypogastric artery. Necropsy revealed metastatic carcinoma in pelvic nodes and superficial inguinal nodes
12. Stqts. 64 years	Yes (12 years and later 6 months previously	No	2/6/51 Portion of pubic arch resected	Previous	—	Recurrence in 3 months. Died in seventh month postoperatively. Necropsy revealed metastases in periaortic nodes, liver, lung, etc.
13. Morg. 60 years	No	No	4/16/51	No	Negative (clinically)	Living, well 56 months after operation. Bilateral moderate hydronephrosis. Serum chlorides slightly elevated; serum CO_2 slightly depressed; blood urea nitrogen slightly elevated. Clinically has no evidence of hyperchloremic acidosis
14. Hen. 52 years	No	No	4/23/53	No	—	Coronary occlusion on fourth day. Necropsy showed no residual cancer
15. Matt. 48 years	Yes	Yes	7/13/54	Yes	Positive	Postoperative atelectasis, shock, icterus, chemical imbalance. Died on fourth day after operation
16. Armst. 68 years	No	No	11/9/54 Poor cardiac risk Anterior exenteration	No	Positive (clinically)	At tend of vulvectomy there were laryngospasms and cyanosis, then cardiac arrest. Could not be resuscitated. Necropsy revealed severe arteriosclerosis (coronaries), myocardial fibrosis, left inguinal node metastases
			11/13/54 Vulvectomy	No	Positive (clinically)	

TABLE II. CARCINOMA OF THE VULVA TREATED BY TOTAL PELVIC EXENTERATION

PATIENT, AGE	PREVIOUS SURGERY	PREVIOUS RADIATION	DATE OF OPERATION	GROIN DISSECTION	INGUINAL NODES	SUBSEQUENT COURSE
17. Mable. 61 years	Yes	Yes	1/2/48	Previously elsewhere	Undetermined	Delayed wound healing, secondary closure of perineal wound, uremia. Died on forty-first day. Necropsy: no apparent cause of death
18. Dix. 44 years	Yes	Yes	12/1/49 Partial resection of ischium and pubic arch	Previously elsewhere	Undetermined	It was felt that disease was left behind. Brief period of palliation. Died of recurrence in 7 months
19. Atk. 63 years	No	No	12/16/49 Portion of pelvic arch resected	No	Positive node in pelvis near sciatic nerve	Recurrences in nodes of both groins. Died of recurrences 3 years after operation
20. Hort. 64 years	Yes	Yes	5/17/51	No	Positive	Postoperative course complicated by thrombophlebitis. Died on eighty-ninth day. Necropsy: acute left pyelonephritis; peritonitis; bronchopneumonia; residual carcinoma in left inguinal region
21. Walw. 52 years	Yes 1 year, 3 months	No	10/15/51 Partial resection of pubic arch	Previously, right side	Negative	Living, well, and working 50 months after operation
22. De Lu. 51 years	No	No	5/15/53 Partial resection of pubic arch. Cutaneous ureterostomies	No	Positive	On the third day blood pressure fell to 0; because of abdominal distention and tenderness, exploratory laparotomy was done with negative findings. General deterioration, small bowel fistula, pyelonephritis. Died on twenty-fourth day. No necropsy.
23. De Nit. 50 years	No	No	1/14/54 Partial resection of pubic arch. Cutaneous ureterostomies	Yes	Positive	Died on twelfth day of massive fatal hemorrhage from deep in operative field.

There were 2 patients who remained in the hospital for periods exceeding thirty days and died:

Small bowel fistula (Case 7), lived 78 days	1
Cerebrovascular accident, 111 days	1
Total	2 patients

This surgical and hospital mortality of 9 patients in a series of 16 represents an incidence of 56.4 per cent.

Of interest is the fact that in 3 instances intestinal fistulas complicated the postoperative course (2 of the small bowel and one ureterocolic implant leak), an incidence of 19 per cent of the series. None of these patients recovered.

The single success (Case 13) is living and well, free from evidence of recurrent cancer, fifty-six months after operation. This patient, previously operated upon, had a lesion involving the anterior vulva, penetrating deeply about the urethra and extending well up in the anterior vaginal wall, penetrating into the vesicovaginal system. Nothing short of an anterior pelvic exenteration could have encompassed this lesion. Groin dissections were not carried out.

The incidence of "cure" in this group was one of 16 patients, an incidence of 6.3 per cent, which is low; however, these cases represent a group of very advanced lesions in a poor-risk group. Two of the patients succumbed shortly after operation of cardiac failure (12.5 per cent of the series).

Total Pelvic Exenteration

There were 7 patients whose lesions were so advanced as to require total pelvic exenteration. These had been previously treated by radiation and surgery, or by surgery alone. Their average age was 55 years.

These cases are summarized in Table II.

The advanced nature of the lesions in this group is attested to by the fact that in 5 of the 7 patients portions of the pubic arch were chiseled away in order to encompass the disease.

The immediate and hospital mortality in this group was also very high, i.e., 4 of 7 patients, or, 57 per cent. One lived three years and died with inguinal node metastases; groin dissections were not done at the original operation.

The single satisfying result (one of 7, i.e., 14 per cent of the series) had had a previous vulvectomy and groin dissection elsewhere eleven months previously. At the time of total exenteration, a portion of the pubic arch was excised (Fig. 1). She remains well and fully active fifty-six months after exenteration.

Posterior Pelvic Exenteration

When vulvar cancer involves the posterior areas and includes the anal region a posterior pelvic exenteration is indicated with sparing of the urinary tract. The latter markedly reduces the immediate operative risk and obviates certain serious complications later, which may occur when the bladder and lower urethra are removed and urinary diversion of one type or another is necessary.

It appears that combined abdominoperineal resection of the pelvic colon combined with vulvectomy (the latter with or without en masse resection of the uterus and vagina) is much better tolerated than anterior or total ex-

TABLE III. POSTERIOR EXTERATION FOR CARCINOMA OF THE VULVA

PATIENT, AGE	PREVIOUS SURGERY	PREVIOUS RADIATION	OPERATION DATE	GROIN DISSECTION	INGUINAL NODES	SUBSEQUENT COURSE
24. Mark 45 years	No	No	8/14/53	No	Negative (clinically)	Terminal status from disseminated breast cancer 16 months after this operation
25. Merna 64 years	Yes	No	9/ 7/51	Yes	Negative (clinically)	Lived for 30 months. Died suddenly of coronary occlusion
26. Kg. 54 years	No	No	7/17/53 Including pelvic lymph node excision	Yes (3 weeks later)	Negative	Living and well 29 months after operation
27. Smith 75 years	No	No	5/18/54 Uterus not resected but lower vagina excised en masse with perineum and rectum. Pelvic nodes not resected	No	Negative (clinically)	Living and well 19 months after operation

enteration due, no doubt, as indicated above, to the sparing of the urinary tract. The patients, after operation, are comparable to those who received only a combined abdominoperineal resection of the rectal colon.

The cases in this group are summarized in Table III.

There was no surgical or hospital mortality. One patient lived for thirty months and died at 72 years of age apparently of coronary occlusion. One is dying at sixteen months of breast cancer and 2 are living and well nineteen and twenty-nine months, respectively, after operation.

Fig. 1.—Photograph of surgical specimen from total pelvic exenteration (Case 21) performed for recurrent carcinoma of the vulva attached to the right pubic arch. One year and two months previously partial vulvectomy and right groin dissection had been done elsewhere.

A, Inferior ramus of right pubic bone. *B*, Portion of carcinoma. *C*, Bladder. *D*, Uterus. *E*, Pelvic colon. The anus is invaded by carcinoma.

The patient is living and well 50 months after operation and has resumed her full physical activities.

Comment

When carcinoma of the vulva, previously untreated, or recurrent after previous treatment by surgery and/or radiation, has reached the stage where anterior or total pelvic exenteration seems necessary to encompass the disease, the situation is precarious at best. In the evaluation of exenteration operations for all types of advanced pelvic cancer between September, 1947, and November, 1954, 23 patients, mostly in desperate straits from extensive

vulvar cancer, were subjected to anterior or total pelvic exenteration with the performance of bilateral ureterocolostomies or wet colostomies in most instances.

The mortality and results for the anterior and total exenterations are summarized below:

Total number	23
Surgical mortality (died within 30 days of operation)	9
Died in the hospital after 30 days	4
Surgical and hospital mortality	13 (57%)
Lived up to 12 months after discharge	5 (21.4%)
Lived 12 to 36 months	3 (13%)
Living and well 50 and 56 months	2 (8.6%)

The instances of posterior exenteration are not included because of the relative safety of this procedure. These cases are summarized in Table III.

From a consideration of the experiences as outlined, the following impressions are derived:

1. Anterior or total pelvic exenteration for advanced vulvar cancer carries a very high risk of surgical and hospital mortality. This is in contrast with the procedures carried out for cancer of the cervix, corpus, vagina, or rectal colon.

2. Bilateral inguinal lymph node excisions should not be done at the time of the exenteration, but at a later date. Both of these steps performed at once seem to constitute more surgery than can be tolerated. Judgment also must be exercised in performance of pelvic lymph node excisions with exenterations in poor-risk patients.

3. Patients should be carefully selected as to general physical status and neoplasms that are not growing too rapidly.

4. The apparent necessity of chiseling through the lower margin of the pubic arch to encompass the disease is in itself not a contraindication to operation since in the survivor for fifty months in the series, this had been performed.

5. In spite of the high mortality and morbidity in this unselected and exploratory series dealing with advanced carcinoma of the vulva, the operation is not to be abandoned for these forms of cancer, because some gratifying successes have been achieved both as to palliation and long survival. The necessity of careful selection of patients and performance of wide inguinal and in some instances deep pelvic node excisions at a second stage is emphasized.

Reference

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PELVIC CARCINOMA FOLLOWING IRRADIATION FOR BENIGN GYNECOLOGICAL DISEASES

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SINCE Deutsch,[1] in 1904, and Ouidin,[2] in 1907, first reported the use of x-ray and radium, respectively, for the treatment of benign uterine bleeding, such therapy has been used extensively throughout the world in the treatment of benign uterine bleeding caused by numerous conditions, including fibroids, endometrial hyperplasia, and endocrine or idiopathic menorrhagia.

Most authors agree on a very high rate of improvement, such as cessation of bleeding and reduction in the size of fibroids.

The question of whether or not these patients treated with irradiation are more likely to develop subsequent gynecological, or pelvic malignancy has arisen and has been studied by many authors. These studies have been from two approaches: first, large groups of patients previously irradiated for benign bleeding have been followed for various periods to determine what percentage subsequently developed gynecological, or pelvic, cancer; second, large groups of patients with uterine and ovarian cancer have been studied to determine what percentage had previously been irradiated for benign bleeding.

Numerous difficulties arise when such studies are attempted. First is the fact that most of the large groups of patients treated with radium and/or x-ray for benign uterine bleeding are followed only long enough to evaluate the primary results such as control of bleeding and possibly reduction in the size of the fibroids. Second, it has been difficult until recently to establish a normal occurrence rate of malignancy in the various viscera for comparison with the treated groups. Third, various other conditions such as menorrhagia and delayed menopause are commonly associated with fibroids or are the symptoms for which the original irradiation was given, and if corpus cancer subsequently develops, these menopausal menstrual disturbances, rather than the previous radiation, are blamed as the predisposing influences.

We have found no report in the literature stating that irradiation for benign bleeding predisposed the patients to an increased chance of subsequently developing corpus, gynecological, or pelvic cancer.

Corscaden[3, 4] has reported on a study of 958 patients treated with irradiation for various benign uterine conditions, with and without abnormal bleeding. He found 22 cases of pelvic malignancy, including 17 cases of gynecological cancer. He stated that all of the subsequent cancers developed in patients who had abnormal bleeding, and concluded that the abnormal bleeding was the predisposing cause of the corpus cancer rather than the irradiation.

Randall[5, 6] studied a large group of women, more than 9 years after the menopause, in whom no cancer of the corpus had developed. Thirteen per cent of these women had had some menorrhagia of the menopause. He compared this group with a group of patients with corpus cancer in approximately 45 per cent of whom menorrhagia of the menopause occurred, and concluded that "when postmenopausal bleeding occurs, the woman with a history of menorrhagia during the climacteric has a 3.5 times greater chance of having developed a fundus cancer than does the woman who experienced no increased bleeding prior to the cessation of her periods."

We have studied a group of 377 patients with corpus cancer treated at Roswell Park between 1947-1952 and found only 14.5 per cent who had any excessive menopausal bleeding (Table I). Since this is so near Randall's 13 per cent menorrhagia in noncancer patients, we must conclude that menopausal menorrhagia does not have the apparent predisposing influence that Randall and Corscaden have claimed.

TABLE I. CORPUS CANCER, 1947–1952, 377 CASES

PREMENOPAUSAL		POSTMENOPAUSAL	
No. of patients	81	No. of patients	296
Average age at onset of corpus cancer	47.4 years	Average age at menopause	49.4 years
Menstruating beyond 50 years	43%	Menstruating beyond 50 years	54%
		Menorrhagia of menopause	43*
		Per cent with menorrhagia	14.5 (±1.22)

*In addition to these 43 cases which we consider as having been true menorrhagia, there were 62 other cases of either irregular or profuse bleeding. However, the very short duration in these cases was such that we felt certain that the abnormal bleeding was a symptom of the corpus cancer rather than an endocrine type of bleeding.

Costolow[7] reported upon 1,000 patients who had been irradiated for fibroids, with and without associated abnormal bleeding, and found only 6 gynecological cancers.

Crossen and Crossen[8] reported upon 2,136 patients with fibroids without irradiation who developed 50 (2.3 per cent) corpus and ovarian cancers and compared them with 526 with fibroids who were irradiated and subsequently developed 5 (1 per cent) corpus and ovarian cancer. They conclude from these studies that irradiation for fibroids lessens the incidence of subsequent uterine and ovarian cancer.

Montgomery and associates[9] have reported 851 cases, of which 526 were diagnosed as dysfunctional bleeding and 325 as fibroids with associated bleeding. These patients subsequently developed 12 (1.4 per cent) gynecological cancers. Discussing this paper, Healy said, "It would appear that the actual incidence of malignant tumors of the corpus as a late complication following intrauterine radium for benign bleeding is too infrequent and questionable to be advanced as an argument in favor of hysterectomy over irradiation as the treatment for this symptom."[10]

Hunter[11] reported on 644 patients treated by irradiation for benign uterine conditions. Only 3 (0.5 per cent) of these patients later developed gynecological cancer.

Speert[12] quoted Werner (1925), Taylor (1932), McFarlane (1932), and Randall (1945) as concluding that pelvic irradiation may be prophylactic against subsequent cancer of the corpus.

Speert studied 270 patients with corpus cancer and found that 21 (8 per cent) of them had had previous irradiation for benign bleeding. The average interval between the irradiation for the benign bleeding and the subsequent diagnosis of cancer was 8.3 years.

Speert also studied 260 patients with ovarian cancers. Nine of these (3.5 per cent) had had previous irradiation for benign bleeding with an average interval of 9.3 years.

A study of 377 corpus cancer patients first seen at Roswell Park between 1947 and 1952 showed that 21 patients had had previous irradiation of the pelvis, 17 for benign uterine conditions and 4 for non-uterine pelvic cancer. The average interval between the irradiation and the subsequent corpus cancer was 11.7 years.

Before 1940, at Roswell Park Memorial Institute, the treatment of benign uterine conditions with radium or x-ray or both was common practice. Since 1940, irradiation for benign bleeding is given only if surgery is contraindicated. This change of policy came with the realization that from time to time a patient who had had irradiation for benign bleeding would return to us with uterine or other gynecological or pelvic cancer.

Realizing the long intervals shown by Speert's and our own studies and, also, realizing the rather short follow-up used in most of the reports in the literature, we have undertaken a study of all pelvic cancer following irradiation for benign uterine conditions occurring at Roswell Park.

Material

Only patients treated prior to 1941 were included in order to give a satisfactory interval in which to consider the development of subsequent cancer. Questionnaires were mailed to 1,670 patients who had been treated between 1930 and 1940 with radium and/or x-ray for benign uterine abnormalities. These were asked:

1. Their opinion as to whether the symptoms were relieved.
2. Whether these symptoms later recurred.
3. Whether any pelvic operation or irradiation was subsequently necessary.

If question 3 was answered "yes," the doctor and/or hospital was then contacted for full data.

Many letters were returned by the Post Office Department labeled "Present Address Unknown." Adequate replies were received from 721 patients. All of these patients were followed for 12 or more years; the average follow-up was 16.08 years.

The diagnoses in these 721 patients were originally as follows:

Fibroids	641
Nonfibroids (hyperplasia, cervical polyps, etc.)	80

Table II shows the results of treatment in these 721 patients.

Age.—Table III shows that the ages at the time of the original irradiation varied from 17 to 80 years. There were 89.11 per cent between 35 and 55; 60.65 per cent between 40 and 50, and the average mean age was 45.41 years.

TABLE II. CLINICAL RESULTS OF RADIATION FOR FIBROIDS OR BENIGN UTERINE BLEEDING

DIAGNOSIS	NO.	GOOD RESULTS	POOR PRIMARY RESULTS	RE-TREATED WITH GOOD RESULTS	SUBSEQUENT SURGERY
Fibroid	641	604 (94.2%)	37	21	16*
Nonfibroid	80	74 (92.5%)	6	6	0

*None of the 16 cases operated upon showed any cancer in the surgical specimen.
One of the 16 had a subtotal hysterectomy and ten years later developed squamous cancer of the cervical stump.

TABLE III. AGE DISTRIBUTION

Youngest	17 years
Oldest	80 years
Average age	45.5 years
Distribution:	
35-55 years	89.1%
40-50 years	60.6%

Treatment.—In some of the very young women with endocrine types of menorrhagia, small doses of radium (800 to 1,100 mg. hr.) were used in an attempt to produce a temporary cessation of menses, with the expectation that the ovaries would recover sufficiently for normal menstruation to recur later.

TABLE IV. METHOD OF TREATMENT

TREATMENT	NO. OF PATIENTS	SUBSEQUENT PELVIC CANCER	
		NO. OF PATIENTS	%
Radium only	88	5	5.2
X-ray only	150	10	5.6
Radium and x-ray	483	46	9.5
Total	721	61	8.4

In the older ages, at or about the menopause, larger radiation dosages were employed to produce a permanent menopause. These dosages varied from 1,400 to 2,400 mg. hr., with the majority of the patients receiving 1,600 to 1,800 mg. hr. or this equivalent when x-ray alone or in combination with radium was used. Table IV shows the number of patients treated by each method with the number and percentage of subsequent cancers.

Subsequent Cancers.—These 721 patients, all of whom were followed for more than 12 years and for an average period of 16.08 years, have developed 61 cancers (8.43 per cent) of the structures within the range of the previous irradiation. These cancers are shown in Table V.

TABLE V. NUMBER OF MALIGNANCIES FOLLOWING RADIATION FOR FIBROIDS OR BENIGN UTERINE BLEEDING AND THE AVERAGE INTERVAL TO THEIR DEVELOPMENT

SITE	NO.	INTERVAL IN YEARS
Corpus	29	9.69
Cervix	11	8.5
Ovary	8	10.1
Rectum	7	10.7
Bladder	3	14.0
Vagina	2	12.7
Vulva	1	14.5
Total	61	9.96 average

All of these patients had curettage and cervical biopsy before radiation. No specimen showed any malignant or premalignant condition. None of the 29 corpus malignancies were sarcoma. Ten of the 29 patients with corpus malignancies did not have abnormal bleeding prior to the original irradiation.

Expected Incidence of Cancer

Cancer has been a reportable disease in New York State (exclusive of New York City) for the past 12 years. The Division of Cancer Control has recently summarized the figures for the years 1949, 1950, and 1951. These figures represent more than 60,000 patients, or 20,000 per year. Approximately 80 per cent of these cases were diagnosed and reported while the patients were alive, and 20 per cent were first reported on death certificates. These figures are given by 5 year age groups for the various anatomical locations. This information allows one to determine the expected incidence or number of cancers of any anatomical location, of any age group, for any period of follow-up.

We realize that such figures as these may be inaccurate because we as physicians are inaccurate in reporting cancer, and inaccurate in filling out death certificates. Even so, we feel that they are accurate enough to be used as a so-called normal incidence or occurrence rate with which to compare our findings, especially because they are for the same area, upstate New York, as are our 721 patients.

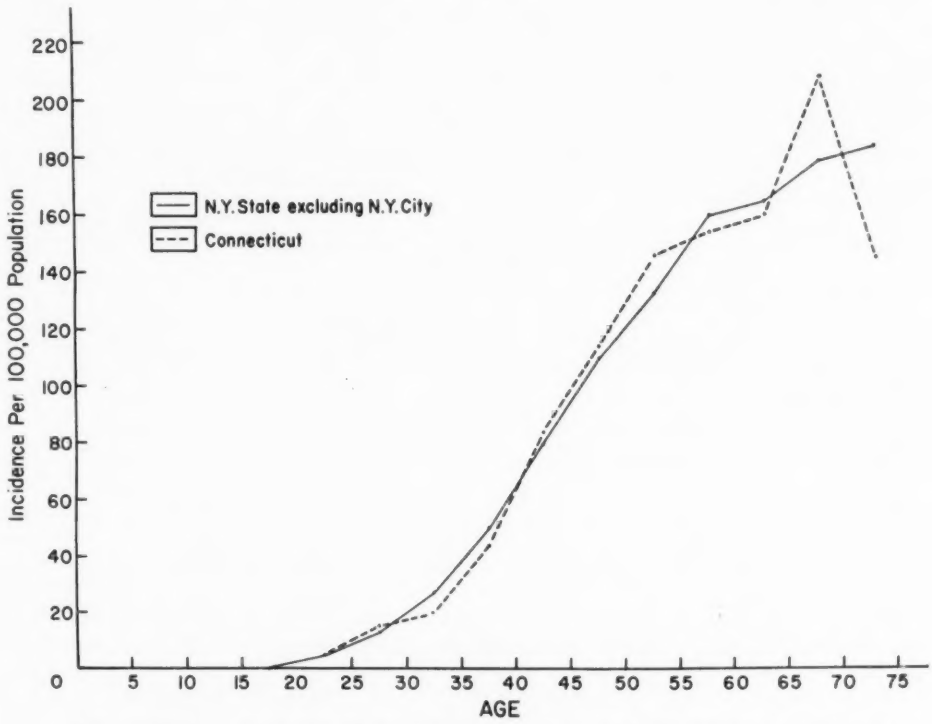

Fig. 1.—Incidence by age of gynecological cancer in Connecticut and New York.

Fig. 1 shows a comparison of the incidence of genital cancers for the various age groups as reported by the Health Departments of New York State and Connecticut. The marked similarity of the two groups is further evidence that the "expected incidence" which we have used is adequate for comparison with our subsequent cancers "found."

Our 721 patients have been divided into 5 year age groups and our statistician has calculated the expected number of cancers that should have occurred in a like number of "normal" women in the same age groups.

Table VI compares the expected number with the actual number of cancers of the viscera or parts within the effective range of the irradiation occur-

ring in the 721 patients. These figures are compared with the expected number and the actual number of malignancies of the breasts, the breasts being out of the effective range of the irradiation. These figures show the ratio of cancers found to those expected to be high in every part irradiated, ranging from a low ratio of 1.53:1 for cervix to 5.95:1 for corpus, to the highest ratio of 11.78:1 for vagina. In the same patients, the breasts, which were not irradiated, showed fewer cancers than would be expected for the age groups normally. We feel that this below normal incidence of breast cancer shows that we were not dealing with an abnormally predisposed group of patients.

TABLE VI. COMPOSITE COMPARISON

SITE	NO. OF CASES FOUND	NO. OF CASES EXPECTED	RATIO FOUND:EXPECTED
Fundus	29	4.86	5.95
Cervix	11	6.53	1.68
Ovary	8	2.58	3.1
Rectum	7	2.11	3.32
Bladder	3	.82	3.66
Vagina	2	.17	11.78
Vulva	1	.33	3.0
Total	61	17.40	3.48
Breast	10	14.3	0.71

Table VII lists the number of cancers of the corpus, cervix, and ovaries occurring subsequently to irradiation for benign conditions as reported by the authors previously quoted.

TABLE VII. CANCERS SUBSEQUENT TO IRRADIATION FOR BENIGN CONDITIONS AS REPORTED BY VARIOUS AUTHORS

	CORSCADEN	COSTOLOW	CROSSEN	MONTGOMERY	HUNTER	ROSWELL PARK MEMORIAL INSTITUTE
No. of patients	958	1,009	526	831	644	721
Followed less than 10 years	78%	Not stated	Not stated	76.8%	65%	0
Subsequent cancer						
Corpus	9	3	4	9	2	29
Cervix	6	2		2		11
Ovary	2	1	1	1	1	8
Total	17 (1.78%)	6 (0.59%)	5 (0.95%)	12 (1.41%)	3 (0.46%)	48 (6.65%)

The number of patients considered, in every group, is sufficiently large to reduce the standard deviation to a minimum. The benign conditions for which these several groups of patients were originally treated were very similar. The age groups showed no appreciable variable. Why is there such a great difference in the percentage of subsequent genital cancers found? The only answer we have been able to arrive at is the difference in the follow-up period.

In a search for the explanation of these findings of an unusually large percentage of subsequent pelvic cancers, we have considered the possibility that these patients may have some endocrine imbalance which could have been a so-called predisposing cause for the subsequent development of genital cancer. Granting this possibility, even though we have found nothing to substantiate it, we can see no possible connection between such an endocrine influence and the unusually high incidence of bladder and rectal cancer which were 3.66 and 3.32 times the normal expectancy. These nongenital sites showed a higher incidence than the cervix.

Influence of Fibroids

Following further the idea of some possible endocrine disorder, we have also considered the possibility that cancer of the corpus could be more frequently found in association with uterine fibroids. A study from this standpoint, however, shows 23 corpus cancers developing in the 651 patients with fibroids, an incidence of 3.6 per cent, and 6 corpus cancers in the 80 patients with benign disorders other than fibroids, an incidence of 7.5 per cent. These findings discount the associated fibroids as a possible predisposing factor.

Influence of Hyperplasia

We next considered the possible influence of "endometrial hyperplasia" in the original specimen as a predisposing influence to subsequent development of corpus cancer.

Some degree of hyperplasia was found in the original curettings of 581 of the 721 patients in this study, approximately 81 per cent. This number and percentage of "hyperplasia" seems rather high, although King[13] has reported 71 per cent hyperplasia associated with fibroids.

We have also discussed the incidence of endometrial hyperplasia with the pathologists in two of the general hospitals in Buffalo. One of these pathologists estimates that, in his nonobstetrical curettings, he finds approximately 50 per cent with hyperplasia. He further estimates that approximately 75 per cent of the curettings from patients with fibroids show hyperplasia. The other pathologist estimates 50 to 60 per cent with hyperplasia when all age groups are considered and approximately 90 per cent with hyperplasia in the 40 to 50 year age group. When these figures on hyperplasia are considered, our 80 per cent incidence of hyperplasia does not seem excessive.

Our study showed 23 subsequent corpus cancers in 581 cases of hyperplasia, 3.94 per cent, and 6 corpus cancers in 140 cases of disorders other than hyperplasia, 4.28 per cent. Thus, hyperplasia in general does not seem to be the predisposing cause of subsequent cancer of the corpus in this group.

A further study of the small group of cases of adenomatous hyperplasia, considered by many authors to be definitely precancerous, shows a very different relationship. Nine patients' specimens were originally classified as adenomatous hyperplasia and 4 (44.4 per cent) subsequently developed corpus cancers. Even in this group the intervals between the radiation treatment and the subsequent cancer, 20 years, 16½ years, 13 years, and 7 years (average 14 plus years) are so long that the relationship may be questioned.

Comparison of Radiation Dosages

We next studied 471 patients with cancer of the cervix treated during this same period (1930-1950). These included all the patients with cancer of the cervix who had survived their cancer for more than 10 years and had been followed for the same average time after irradiation, 16 years, as had the patients treated for benign bleeding. The average age at the time of irradiation of the patients with cervix cancer was slightly higher than that of those treated for benign bleedings, but the slight difference was not considered to be significant.

With very few exceptions, all of the patients with cervix cancer were treated with radium and x-ray. In these 471 patients with cervix cancer, 13 pelvic cancers (2.75) developed following irradiation. The shortest interval was 8 years, the longest 21 years, the average was 13.8 years. Table

VIII lists these subsequent cancers by anatomical sites, compared with the number that would have been expected, using the same New York State Health Department expectancy rates.

TABLE VIII. CERVIX CANCER, 1930–1940, 471 CASES

SITE	NO. FOUND	NO. EXPECTED	RATIO
Corpus	3	3.2	.94
Cervix	3	4.3	.70
Ovary	1	1.7	.59
Vagina	2	.11	18.2
Vulva	1	.22	4.5
Rectum	2	1.4	1.4
Bladder	1	.5	2.0
Total	13	11.43	1.14
Breast	4	9.4	.43

In this group of patients with cervix cancer who had a relatively high radiation dosage, the ratio of subsequent pelvic cancers found to the number expected was 1.14 times normal, compared with 3.48 times normal in the benign-bleeding group who had had a low radiation dosage. This finding raises the very interesting question of a possible stimulating, or growth-inducing, influence of a relatively low dosage of irradiation.

Table IX shows the comparison of dosages in the patients with benign disease and those with cervix cancer. The dosage for the cervix cancer was 2.26 to 2.66 times the dosage for benign lesions.

TABLE IX. RADIATION DOSAGE

	2 CM.	5 CM.
Benign, average	2,700 r.	650- 700 r.
Cervix cancer, average	6,500 r.	1,500-2,000 r.
Dosage ratio, benign:malignant	1:2.66	1:2.26-1:2.28

Conclusions

1. Irradiation for benign uterine bleeding is symptomatically effective in a very high percentage of the patients treated.

2. Since our incidence of subsequent pelvic cancers is higher than any previously reported, we must conclude that the authors quoted from the literature have not used a long enough follow-up time for such a study.

3. We have found a rather low incidence of menorrhagia of the menopause in our patients with corpus cancer and must conclude that the menorrhagia, or its underlying cause, is not a significant predisposing influence in the development of subsequent malignancy of the corpus.

4. In the absence of any other known influence predisposing to the development of subsequent cancer in this large group of women, we have reason to believe that the previous irradiation is, at least in part, responsible for the subsequent cancers. Also, since the patients with controlled cancer of the cervix did not show the high incidence of subsequent cancer of the adjacent pelvic structures, we believe that the relatively low irradiation dosage given the group with benign lesions has caused some growth-stimulating influence that the higher, cancerocidal dosage does not cause.

5. Finally, we must conclude that irradiation castration should be used only in women who are not satisfactory surgical risks and, if used, should probably be given in adequate dosage to overcome the possible growth-stimulating influence.

Addendum.—Since this paper was written we have continued the study of this subject. We have received 20 additional replies indicating no disease subsequent to the original irradiation. We have also seen 9 patients who had developed 10 subsequent pelvic malignancies (one patient having a coexistent squamous-cell carcinoma of the cervix and adenocarcinoma of the rectum). Five of these patients had not answered their questionnaires. Thus we add 25 patients to the 721 originally studied and add 10 pelvic cancers to the 61 reported.

These cancers include: cervix, 4; ovary, 3; corpus, 2; and rectum, 1.

The shortest interval after the original radiation treatment was 13 years and the longest 23 years; the average interval was 17.3 years.

We wish to acknowledge the valuable help given by the Gynecological Pathology Department in reviewing the histology of all the original specimens as well as the specimens on which the subsequent diagnosis of malignancies was made.

We wish also to acknowledge the help of Dr. Grace Marie Waldrop for proofreading and arrangement of the bibliography.

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PROCEDURE FOR THE REDUCTION OF THE NUMBER OF URETEROVAGINAL FISTULAS AFTER WERTHEIM'S OPERATION

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DURING the years from 1920 till 1953 there occurred in our department 63 cases of ureterovaginal fistulas following 618 Wertheim's operations (10.19 per cent). In the last two years, after adopting some small and very simple modifications in the technique of Wertheim's hysterectomy, we had only 1 fistula in 100 such operations.

Facts on Which Our Procedure Is Based

Ureteral fistulas are caused by several factors. We shall discuss only those factors that can be controlled by means of accurate and proper technical procedure.

1. These fistulas always appear in the region between the uterine artery and the bladder. They occur almost invariably without any previous visible injury of the ureter and are due to subsequent ureteral necrosis.

During the dissection of that part of the ureter that passes through the parametrium we sometimes see that in spite of the most careful dissection the fine covering of the ureter slips downward toward the bladder. Such an exaggerated circular denudation of the lower part of the ureter is dangerous.

After Schauta's radical vaginal operations, there are significantly fewer fistulas than after Wertheim's operation. The terminal region of the ureter is traumatized and subject to infection in both operations but in Schauta's one side of the ureter remains in better contact with the bladder.

The first conclusion is, therefore, that to prevent fistulas, it is necessary to prevent circular denudation of the ureter from the level of the uterine artery downward.

2. In operations performed for ureterovaginal fistulas we have noticed that the ureter does not lie where we left it at the end of the Wertheim operation. Instead we find it has been drawn toward the pelvic wall by scars, which are the cause of a kink in the ureter. Moreover, the terminal part of the ureter between the pelvic wall and the bladder is found distended, a condition which interferes with the discharge of the urine.

The assumption that this kink of the ureter is also one of the factors causing fistula formation is supported by the experience of urologists in ureterolithotomy. After the removal of the stone, the cut on the ureter heals without any stitching, whenever the discharge of the urine is free. If, however, the passage for the urine is obstructed, the fistula appears in spite of stitching of the ureter.

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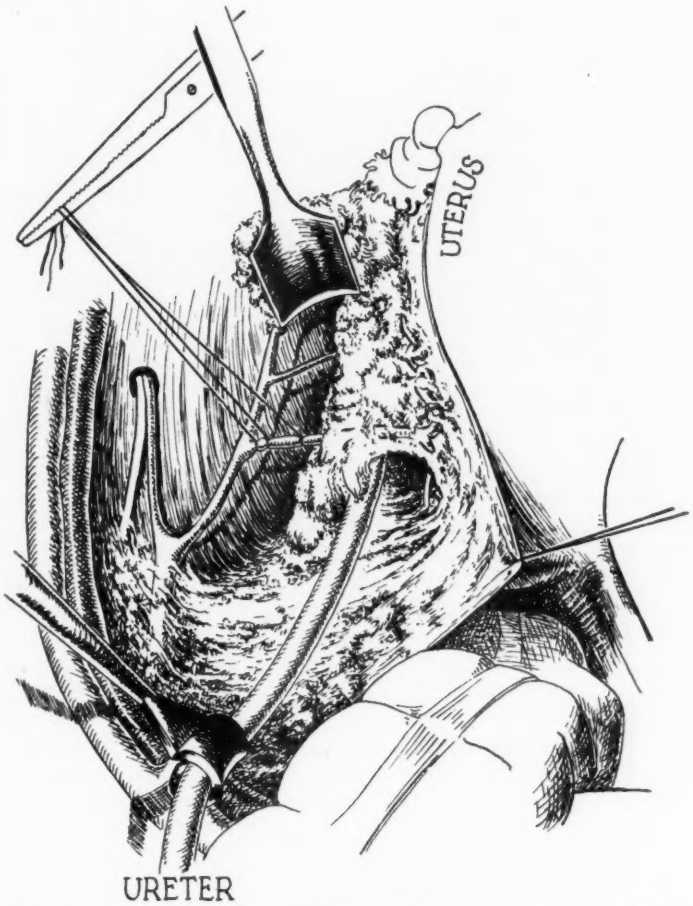

Fig. 1.—The uterine artery is isolated and ligated at its origin from the hypogastric artery, but is not divided.

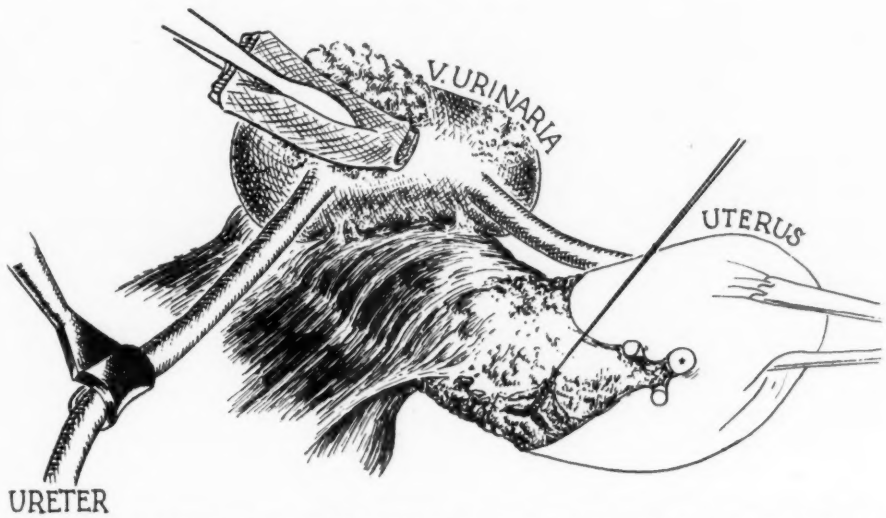

Fig. 2.—If the uterine artery is divided first and the channel and the ureter are dissected at this time through the parametrium, the fine vessels which attach the periureteral plexus of vessels to the ureter may be torn off. The periureteral tissue then slips toward the bladder and the ureter remains circularly denuded.

Conditions after the juxtavesical ureterolithotomy are, however, essentially different from those after Wertheim's operation. At the ureterolithotomy we do not remove the surrounding tissue and the ureter unites with it again. After Wertheim's operation the ureter passes through spaces with injured walls. We believe the ureter should not be placed in such potentially infected cavities, full of coagula, dead tissues, ligatures, and drains.

The second conclusion is that to prevent fistula formation it is necessary to prevent kinking in the terminal region of the ureter.

With our procedure we believe we have succeeded in avoiding the denudation of the terminal portion of the ureter and the obstruction of urinary flow resulting from kinking.

The Technique of Radical Hysterectomy With Bilateral Dissection of Nodes With Stress on Our Modifications

After Schiller's test of the vagina, a large lower midline incision, palpation of the upper abdomen, presacral neurectomy according to Cotte, and full pelvic lymphadenectomy from the aorta downward on both sides, we isolate and ligate the uterine artery at its origin from the hypogastric artery, but we do not divide it till later. Then, we entirely free the proximal part of the ureter but below its entrance into the parametrium denude it only on the mediodorsal side. We push the closed scissors along the ureter on this mediodorsal side and thus create a space by means of careful blunt dissection (Fig. 1). The same procedure is carried out on the opposite side.

After separation of the vagina from the rectum and development of the subrectal fossas, we cut the superficial as well as the deep layers of the uterosacral ligaments on both sides, but do not divide the cardinal ligaments at this time. If we cut the cardinal ligaments before complete freeing of the ureter, our procedure is not possible.

With the right and left uterosacral ligaments cut, but with the cardinal ligaments still in place, we begin to free the distal part of the ureter. We incise the roof of the ureteral channel medial to the ureter and close to it, thus freeing the mediodorsal side of the ureter and separating it together with the bladder from the cervix and vagina.

If the uterine artery is divided first, as is the usual custom and the channel and the ureter are dissected through the parametrium at this time, the fine vessels which attach the periureteral plexus of vessels to the ureter may be torn off. The periureteral tissue then slips toward the bladder and the ureter remains circularly denuded (Fig. 2). In order to prevent this we use the uterine artery as a sort of suspender. By means of this we prevent circular denudation of the ureter from the uterine artery downward.

Only after this step is completed do we divide the uterine artery at its origin from the hypogastric artery. By following these steps in this order the periureteral tissue is preserved on the lateroventral side of the ureter. This tissue we call the "little roof" (Fig. 3).

With the lateroventral attachments of the ureter thus preserved, the vesicouterine ligaments are cut and the separation of the bladder is carried further downward. The cardinal ligaments are clamped near the pelvic wall and the specimen is removed.

In reperitonization of the pelvis we do not place the ureter retroperitoneally, as is usually done, but locate it intraperitoneally from the point where it crosses the common iliac artery downward (Fig. 4). Thus we prevent the retraction of the ureter toward the pelvic wall and avoid the kink in its terminal region. Besides this, we put the ureter in an uninjured, uninfected, vital environment which is without coagula or necroses.

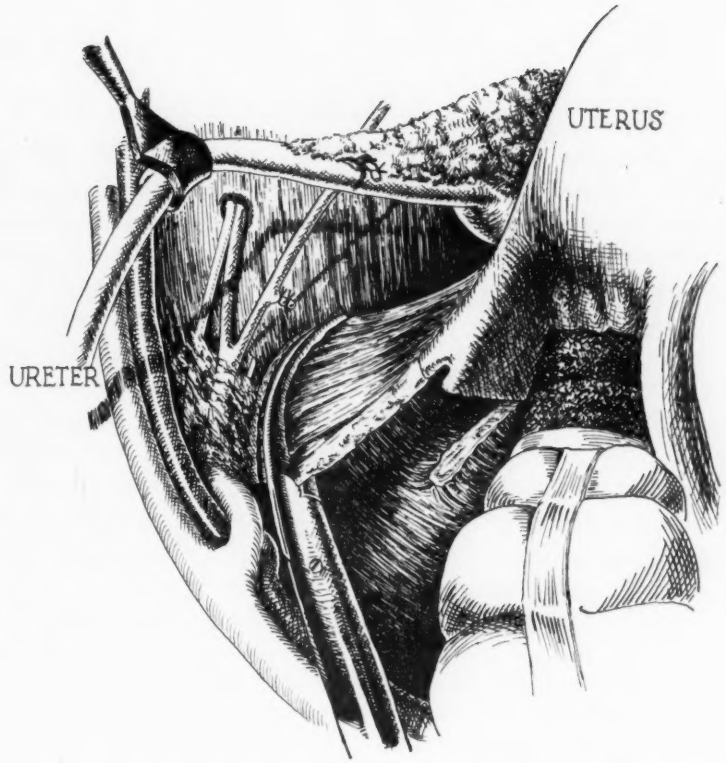

Fig. 3.—The periureteral tissue is preserved on the lateroventral side of the ureter.

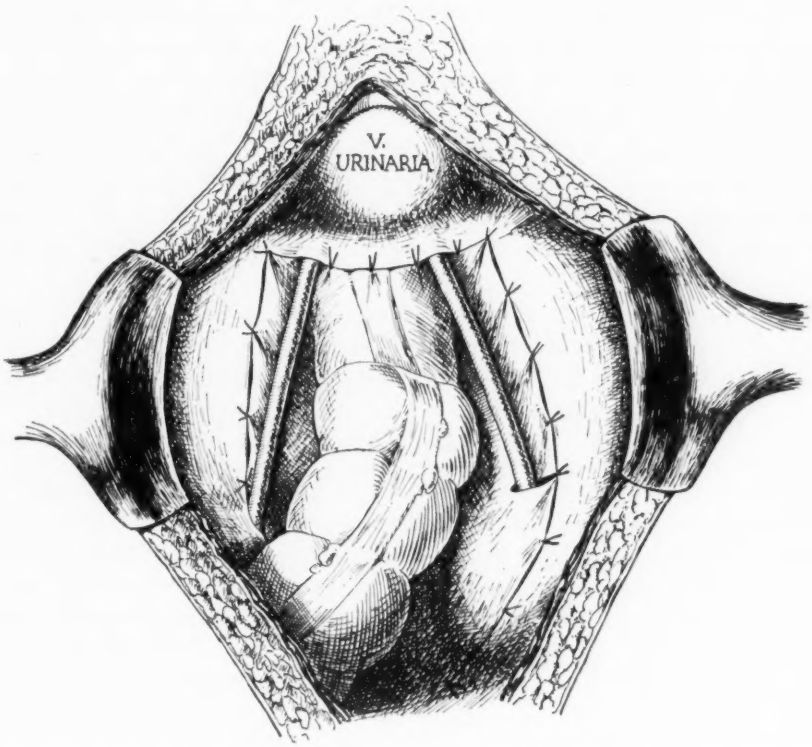

Fig. 4.—In reperitonization of the pelvis, the ureter is placed intraperitoneally from the point where it crosses the common iliac artery.

Comment

In a case of carcinoma radicalism is of course the first principle to be observed. In our procedure we prevent the circular denudation of the ureter from the uterine artery downward, but the ureter is completely denuded only on the side which is nearest to the carcinoma. On the lateroventral side of the ureter the periureteral tissue is preserved. This is perhaps the weakest point in the procedure. With the requirements of radical surgery in mind, however, this method is better than leaving tissue completely around the ureter in order to avoid its sloughing.

The conditions created are similar to those after Schauta's operation. No one has yet questioned the radical character of Schauta's vaginal operation simply for the reason that the lower part of the ureter remains in closer connection with its areolar tissue and the bladder than in Wertheim's procedure. The only criticism voiced against Schauta's operation was that it did not include a pelvic lymphadenectomy.

In the "little roof" of the ureter the fine collateral circulation is preserved in the branches of the bladder vessels which anastomose with the uterine artery. Too much stretching and pulling of the "little roof" and of the distal part of the ureter must be avoided so as not to tear the fine vessels attaching the "little roof" to the ureter.

The circular freeing of the upper part of the ureter is without danger. Usually in our operations about 18 cm. of the right and about 15 cm. of the left ureter are denuded. In the only fistula that we have had no bad consequences from the intraperitoneal position of the ureter were observed. It appeared on the twenty-fifth day with the usual signs.

Our cases were not selected. There were examples of Stages I, II, and III, and 14 times we operated after radium and x-ray therapy. Four times we had recourse to the Logotetopulos tampon and in all other cases a subperitoneal gauze pack was applied on both sides. The lower end of the gauze was brought out through the vagina and removed in 48 to 72 hours by pulling on the free end.

The importance of the modification is perhaps not only in prevention of fistulas. We also hope to reduce the later strictures of the ureters which often occur, which would be important since so many of these patients eventually succumb to uremia.

Summary

With the usual technique for radical hysterectomy, in a former series of over 600 operations, ureterovaginal fistulas occurred in about 10 per cent of the cases. With some simple modifications of technique the number of fistulas has now been sharply reduced.

The procedure prevents, first, the circular denudation of the distal part of the ureter, creating conditions similar to those after Schauta's radical vaginal hysterectomy, and, second, assures a free flow of the urine because it prevents the kink that commonly develops in the terminal region of the ureter.

A COMPARATIVE STUDY OF DIFFERENT TECHNIQUES FOR THE DIAGNOSIS OF CERVICAL CARCINOMA

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(From the Cytology Center, Beth El Hospital)

THE conflicting reports on the number of cases of cervical carcinoma detected by exfoliative cytology are accumulating in the literature. The reasons for marked differences in the statistical data are slowly crystallizing. It seems that various population groups yield different figures depending on racial and social factors, as well as whether early circumcision of the male is practiced in the population group under investigation. Different racial ratios and the difference in the age group predominantly available for examination may greatly alter the rate of over-all prevalence of cervical carcinoma. Even under otherwise constant conditions, an investigation may produce conflicting results if different techniques are applied in the taking of cytological specimens.

At present, different methods are used by various investigators for the diagnosis of cervical cancer, such as aspiration from the posterior fornix or cervical os. The use of a cotton applicator has been advocated to prepare a vaginal smear without the use of a speculum by some investigators, while others recommend preparation of the endocervical smear by insertion of the cotton applicator into the cervical canal. Ayre devised a special type of spatula for scraping the cervix, while others recommend a wooden tongue depressor cut at the end with curved scissors.

Method

In this investigation, three techniques have been compared in 154 patients, including 73 cases of different epithelial lesions of the cervix. A cotton applicator was used to prepare a smear from the posterior fornix (Fig. 1). The endocervical smear was made by insertion of the cotton applicator into the cervical canal and twirling it around a few times against the squamocolumnar junction (Fig. 2). The smear is made by rolling the cotton applicator in the counterclockwise direction on the slide in order to secure complete transfer of the cervical mucus plug to the glass. Earlier observation pointed to the fact that rolling of the cotton applicator in the same direction in which the applicator is led on the slide resulted in adherence of the mucus to the cotton material.

The third technique employed was the use of Ayre's wooden spatula for the scraping of the cervix without prior removal of the mucus plug (Fig. 3). This study was carried out in two parts. In the first series the endocervical smear was taken first with the wooden spatula and then with the cotton applicator. In the second series the procedure was reversed.

Results

The first series included 19 cases of cervical carcinoma with 15 in the in situ phase and 19 cases of various degrees of epithelial dysplasia. The smears taken with the spatula contained cancer cells in all 19 cases, while the use of the cotton applicator failed to reveal the cancer in 2 cases.

In the second series, 28 cases of cervical carcinoma were diagnosed by the application of the cotton swab with the utilization of the mucus plug. The total number of positive cases in this group consisted of 25 cases of carcinoma in situ and 4 cases of early invasive cancer. The one case missed with the cotton applicator was diagnosed as cellular dyskariosis. All 6 cases of epithelial dysplasia were correctly reported (Table I).

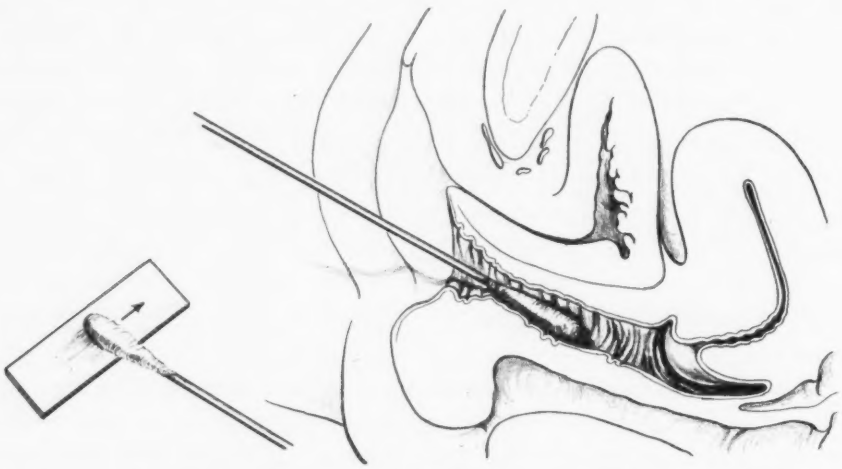

Fig. 1.—Preparation of smear from posterior fornix with cotton applicator.

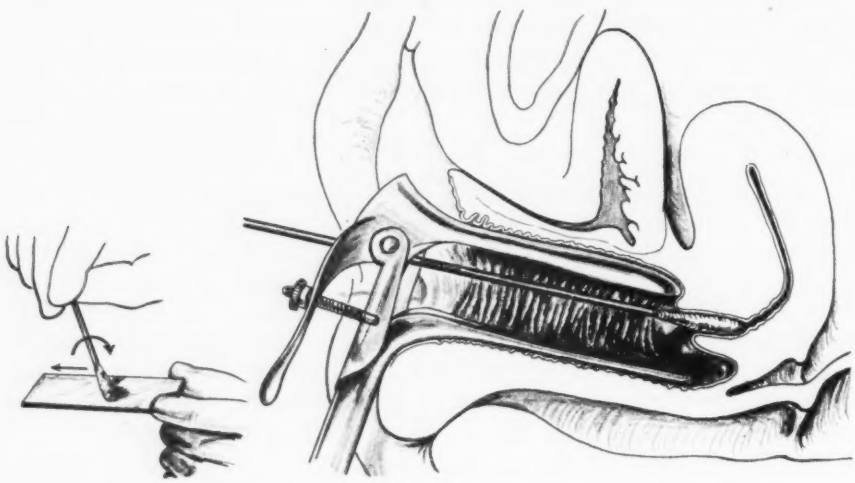

Fig. 2.—Preparation of endocervical smear with cotton applicator.

The use of the Ayre spatula in this group of patients resulted in the diagnosis of only 24 cases of cervical carcinoma. Of the 5 false negative reports, 3 were diagnosed as cellular dyskariosis while 2 were entirely negative.

TABLE I. COMPARATIVE STUDY OF THREE TECHNIQUES FOR THE DETECTION OF CERVICAL CARCINOMA

	SERIES I		SERIES II		
	AYRE'S SPATULA	COTTON APPLICATOR ENDOCERVIX	COTTON APPLICATOR POSTERIOR FORNIX	COTTON APPLICATOR ENDOCERVIX	AYRE'S SPATULA
Cancer cells present	19	17	15	28	24
Dyskariosis	15	18	6	7	9
False negative (dyskariosis)	4	1	-	-	2
False negatives (cancer)	0	2	14	1	5

The smears taken from the posterior fornix resulted in 14 false negative diagnoses.

In the cases of cervical carcinoma, the number of cancer cells present was usually considerably greater in the spatula smears and they were more readily detected (Fig. 5). The negative cases examined by spatula smears contained a larger number of endocervical cells and leukocytes which required a period of screening at least 3 times as long as the cotton applicator specimens (Figs. 4 and 6).

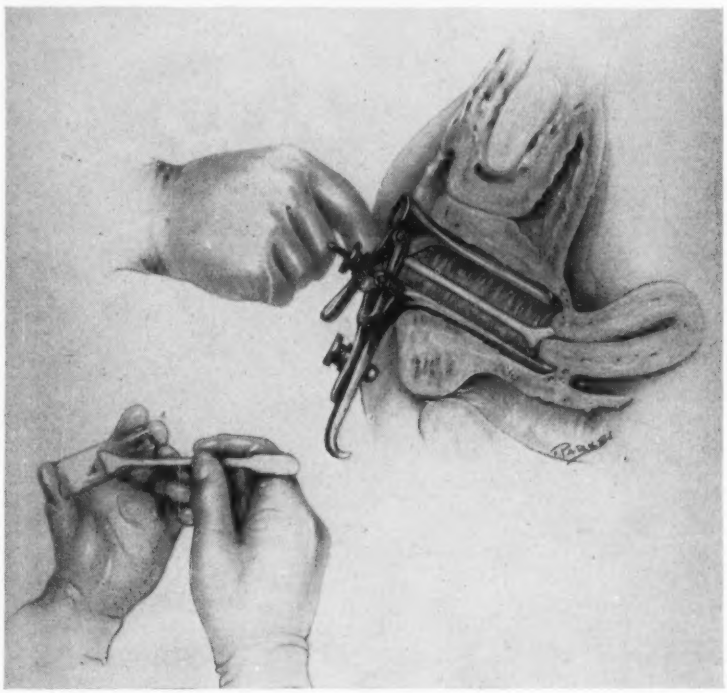

Fig. 3.—Preparation of cervical smear with Ayre's spatula.

Comment

The comparison of 3 different techniques used for obtaining cytological specimens from the cervix showed that the most important factor in achieving

Fig. 4.

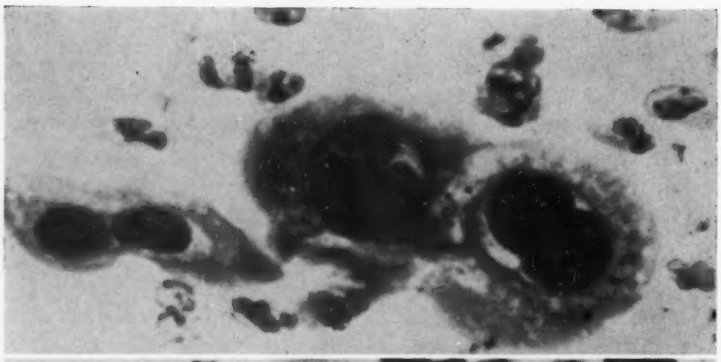

Fig. 5.

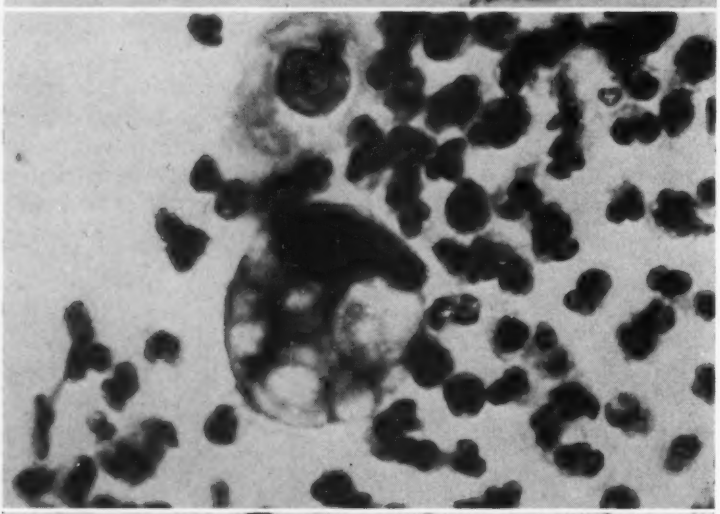

Fig. 6.

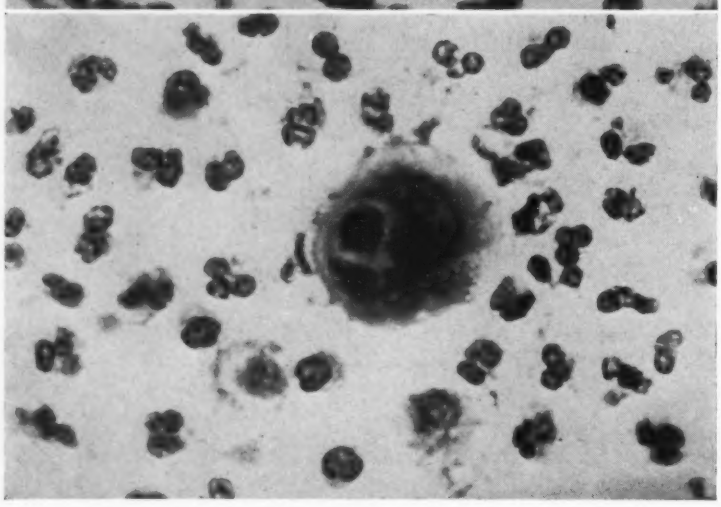

Fig. 4.—Cancer cells in smear prepared with cotton applicator.
Fig. 5.—Cancer cells prepared with Ayre's spatula.
Fig. 6.—Cancer cells in posterior fornix in swab smear.

the greatest accuracy is the utilization of the cervical mucus plug. Smears taken from the posterior fornix, therefore, result in a very large number of false negative diagnoses. It has often been observed that several smears taken from a patient at one examination may differ in their content of malignant cells up to the point of complete absence. Thus, the distribution of several smears to different laboratories often leads to various interpretations, mainly due to the difference in the amount of cervical material present, and constitutes an unreliable method of comparing diagnoses.

The greater number of false negative reports from spatula smears in the second series is apparently due to the fact that the cotton tip inserted into the cervical canal permits a more complete removal of the cervical mucus plug than the spatula. When the spatula is used as the second procedure the complete absence of endocervical mucus may therefore also result in the absence of cancer cells in the smear.

Summary

Statistical data on the incidence of cervical carcinoma diagnosed by cytological methods depend not only on racial, social, and other factors, as well as the predominance of certain age groups, but also on the techniques employed.

Three methods were used in this study: the cotton applicator for the vaginal smear from the posterior fornix, the cotton applicator for the endocervical smear, and the Ayre spatula for the cervical smear.

The smear from the posterior fornix is less satisfactory than those obtained from the endocervix. The occurrence of false negative smears obtained from the endocervix seems to depend on the order in which the smears are taken. The first smear made appears to be the more satisfactory, apparently because of the fact that the endocervical mucus plug was utilized which usually carries a larger number of cancer cells. Smears obtained with the cotton applicator or spatula following the removal of the mucus plug may result in false negative slides. Although in positive cases the spatula smears contain a larger number of cells, for routine cancer detection the cotton applicator smears appear to require less time for the interpretation of slides.

PRESENT STATUS OF PLASTIC OPERATIONS ON THE FALLOPIAN TUBES

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TWENTY years ago, May 8, 1936, before the Chicago Gynecological Society, I read a pessimistic article, published in this JOURNAL, about operations on the Fallopian tubes for the purpose of overcoming obstruction. The basis for my pessimism was the fact that only 54 pregnancies followed 818 plastic operations, performed by specialists in gynecology in the United States. This is only 1 gestation (6.6 per cent) after every 15 operations. Since only 36 live babies were born, however, the incidence of gestational success following these operations was only 1 (4.4 per cent) in 22.5, a very poor showing indeed. Ten, or 18.5 per cent, of the 54 pregnancies ended in abortion, and 8, or 14.8 per cent, were tubal pregnancies. Hence, only two-thirds of the 54 pregnancies resulted in live children, and one-seventh of the women who become pregnant had to have second laparotomies because of tubal pregnancies.

That previous article of mine has been cited in the literature many times. In recent years my pessimism has been supported by some gynecologists and contradicted by a few others whose results were far better than those observed many years ago. Because of these diverse attitudes I again studied the published and unpublished results of plastic operations performed on the Fallopian tubes during the last few years. To obtain new data I reviewed the literature for reports of at least ten such operations, and also wrote to gynecologists who are especially interested in developing techniques for improving the results of such surgery. I have not separated the various types of surgery done, first, because I wanted to learn the over-all results of all types of tubal plastic operations and, second, because often a different operation is done on each tube and even two techniques are performed on the same tube. Under such circumstances it is impossible to determine which deserves credit for a subsequent pregnancy.

All of the articles reviewed, as well as the personal communications (see Table I), were by and from gynecologists especially interested in performing operations on the Fallopian tubes which would enable women to become pregnant. Nearly all of these surgeons have had a relatively extensive experience with this type of surgery, especially since such surgery is not performed frequently.

From the foregoing sources I collected data of 2,113 plastic tubal operations following which there were 405 pregnancies, an incidence of 19.1 per cent, or 1 pregnancy after every 5 operations. Less than 313 live babies were born, however; hence the frequency of living children at most was 77.3 per cent, and only 15.1 per cent for all the operations done, or 1 baby for every 6½

operations. In many of the reports in the literature, and even in some of the personal communications, the outcome of many pregnancies could not be determined. When the end result was not stated I listed the outcome as a live child. I also included the few stillbirths in this group. Hence, the figure of 15.1 per cent is somewhat too favorable for the end results.

Only 11, or 30 per cent, of the surgeons and surgical teams who reported the 37 series of cases listed in Table I have thus far been able to help 25 per cent or more of the surgically treated women to become pregnant, and only 5 of the surgeons reported a gestation rate of more than 33 per cent. The frequency of pregnancy for the entire group varied from 7 to 53.8 per cent.

TABLE I

AUTHORS	NO. OPERATIONS	NO. PREGNANCIES	% PREGNANCIES	% INTRAUTERINE PREGNANCIES	% ECTOPIC PREGNANCIES	% LIVING CHILDREN OF ALL PREGNANCIES	% LIVING CHILDREN OF ALL OPERATIONS
Ahumada and Chevalier	12	2	16.7	16.0		50.0	8.3
Alvarez-Bravo	40	11	27.5	22.5	18.2	63.6	17.5
Beecham	37	17	45.9	43.2	11.8	94.5	43.2
Bohm and Englund	46	8	17.4	8.7	50.0	37.5	6.5
Bunster	92	17	18.5	17.4	5.9	76.5	14.1
Buxter and Southam	35	2	5.7	5.7		100.0	5.7
Carter, Turner, Davis, and Hamblen	22	3	13.6	13.6		100.0	13.6
Castallo and Wainer	93	19	20.4	19.4	5.3	84.2	17.2
Comninos	37	6	16.2	13.5	16.7	83.3	13.5
De Moraes	14	2	14.3	14.3		100.0	14.3
d'Ingianni and Fontenelle	16	3	18.8	18.8		100.0	18.8
Grant and Mackey	114	28	24.6	21.9	10.7	78.6	19.3
Green-Armytage	22	6	27.3			83.3	22.7
Guerrero	36	9	25.0	19.4	22.2	55.6	13.9
Hartnett and Hartnett	21	5	23.8	19.0		80.0	19.0
Hellman	20	3	15.0	15.0		100.0	15.0
Ingersoll	23	3	13.0	13.0		100.0	13.0
Johnstone	27	8	29.6	25.9	12.5	62.5	18.5
Kviz	27	6	22.2	18.5		83.3	18.5
Langley	32	7	21.9	18.8	14.3	57.1	12.5
Martius	65	34	52.3	52.3		100.0	52.3
Murray	86	22	25.6	21.0	18.2	68.2	17.4
Mulligan, Rock, and Easterday	164	25	15.2	11.6	24.0	60.0	9.1
Palmer	200	38	19.0	16.0	15.8	84.2	16.0
Palmer	13	7	53.8		14.3	85.7	46.2
Pasca	202	17	8.4	6.9	17.6	52.9	4.5
Pommerenke	37	5	13.5	13.5		40.0	5.4
Pratt	41	9	22.0	22.0		66.7	14.6
Read	114	10	8.8	7.0	20.0	80.0	7.0
Rutherford, Lamborn, and Banks	43	21	48.8	48.8		85.7	41.9
Snaith	71	5	7.0	7.0		100.0	7.0
Stabile	25	4	16.0	16.0		100.0	16.0
Traenckner	52	8	15.4	9.4	37.5	50.0	7.7
Vltavsky	18	3	16.7	11.1	33.3	66.7	11.1
Weiner	12	3	25.0	25.0		100.0	25.0
Westman	155	12	7.7	7.7		100.0	7.7
White	49	17	34.7	32.6	5.9	64.7	22.4
Total	2,113	405	19.1		15.7	77.3	15.1
Siegler and Hellman	2,285	513	22.6	20.4	9.1		16.6

The incidence of living babies from pregnancies following these operations was distinctly less. Whenever the number of living babies was specifically stated, this incidence varied from 4.5 to 46.2 per cent. Only 5 authors reported 25 per cent or more living children. Are we justified in recommending abdominal surgery when we cannot promise these women more than 1 chance in 4 of having a live baby? Also, we must be honest enough to tell these patients that following this type of surgery the likelihood of a tubal pregnancy, requiring another operation, is increased.

I was able to collect data concerning ectopic pregnancies in 286 gestations, or 70.6 per cent of all the pregnancies. There were 45 ectopic gestations, an incidence of 15.7 per cent. Even if we assumed that there were no ectopic gestations in the remainder of the cases, the incidence would be 11.1 per cent.

Siegler and Hellman Survey

Siegler and Hellman made a most extensive survey of plastic tubal operations. Their survey deserves special consideration because it is a careful analysis of an enormous number of data from a large number of American and foreign gynecologists who have performed plastic tubal operations. In their final analysis they limited their study to the 84 gynecologists who had performed at least 10 tuboplastic procedures. Many of the surgeons listed in my table are also included in Siegler and Hellman's statistics. I agree with Siegler and Hellman that at least 10 operations must be done to familiarize the surgeon with the general technique and pitfalls of salpingoplasty. A total of 2,285 operations were performed, followed by 513 pregnancies (22.6 per cent) but only 378 live births (16.6 per cent). Furthermore, 47 of the women who became pregnant had ectopic pregnancies, an incidence of 9.1 per cent. Siegler and Hellman say: "There is no definite proof that tubal surgery predisposed the patient to subsequent tubal pregnancy." I disagree with this statement because I believe that the incidence of 9.1 per cent is far greater than occurs in women not subjected to tubal operations. This fact must be considered when the decision to operate on occluded tubes is made.

My pessimistic paper of 1936 showed that 66.7 per cent of the women who became pregnant had live children. Twenty years later Siegler and Hellman's analysis shows that this figure has risen only to 73.5 per cent.

This relatively low incidence of success was obtained by surgeons who are skilled in this type of surgery. Therefore it is reasonable to deduce that gynecologists and general surgeons who only rarely perform plastic tubal operations will obtain fewer successes and perhaps higher incidences of ectopic pregnancies. We must also remember that skillful restoration of tubal patency is not the entire answer to overcoming sterility because many women whose tubes are made patent do not conceive. Something else no doubt is important. Also, we must bear in mind that not infrequently a pregnancy occurs in women in whom the tubal patency tests show occluded tubes. Therefore, before one resorts to an operation for relief of tubal obstruction two Rubin tests (the second preferably after the use of antispasmodics) and a hysterosalpingogram should be made. Even in cases where these three tests have showed tubal closure, gestation has occurred. We have much to learn about tubal closure, hence we should be careful and deliberate in our selection of candidates for surgical relief of occluded tubes.

Relationship of Tube to Ovary

Most likely better results following plastic tubal operations can be obtained by careful attention to the physical relationship of the ovary to the re-

paired tube. Hartman pointed out that in the rabbit the fimbriae do not cover the ovary unless the animal is in heat, but as ovulation approaches the fimbriae move considerably. In the hen infundibular motility is so tremendous that it can pick up a yolk out of the body cavity; in fact, it can pick up a cork of the same size and run it through so that the cork will be inside the egg. Westman studied the mechanism which controls transport of the ovum in the rabbit and monkey and found that in both animals the mechanism was about the same. The blood-filled fimbriae expand over the ovary which rotates around its longitudinal axis and the fimbriae are slowly swayed to and fro above the medial and lateral surfaces of the ovary. He made the same observation in the human being. Once he distinctly saw the tube taking up the bursa position and the ostium of the tube swaying to and fro above the surface of the ovary. He believes that a joint activity of the ovary and tubes controls the transport of the ovum.

Blandau showed that in the rat and rabbit the fimbriated end of the tube regularly engulfs the ovary at the time of ovulation. By means of ingenious experiments he can demonstrate at will the activity of the fimbriated end of the tube at the time of ovulation. This action is as follows: Immediately after the ovum is expelled from the follicle it is grasped by the fimbriated end of the corresponding tube and quickly forced into the lumen of the tube just as a person manipulates his lips in eating extremely cold food. Further progress of the ovum in the tube depends on both tubal muscle peristalsis and ciliary action.

Doyle studied tuboovarian physiology at the time of ovulation in 7 women by culdoscopy. In 2 women the tubes were elongated and lay in the cul-de-sac, but no apposition to the ovary or sweeping or grasping motions were noted. Doyle suggests that the ovum migrates to the cul-de-sac by simple flotation and is then siphoned into one of the tubes by peristaltic action. It is possible that in Doyle's patients the anesthesia may have been a factor in preventing tubal activity. Blandau, during his early studies on direct observation of ovulation, discovered that ovulation failed to occur in anesthetized animals. When he sectioned the spinal cord high up ovulation took place. Doyle wrote me, however, that ovulation in the human being is not necessarily inhibited by anesthesia. He saw the ovary grasped by the tube with firm suction on the mediosuperior aspect, although the follicle was in the lateroinferior aspect of the ovary. He also saw the rectum, parametrium, or ovaries grasped by the tube in a fortuitous manner.

Considerable study is necessary to establish whether or not the fimbriated ends of the tubes in women act as they do in the rat, rabbit, and monkey. Even if such an occurrence is not a regular one it seems logical to conclude that the fimbriae do play an important role and therefore should be preserved, whenever possble, at the time of tubal surgery. Furthermore, the corresponding ovary should be placed as close as possible to the fimbriated end of the tube. In women with hydrosalpinx who no longer have any fimbriae, it is certainly imperative to bring the ovary and new tubal orifice as close together as possible. Doyle informed me that he has observed sequential tubal growth after denervation of the tube. He suggests that a tubal denervation be done on the opposite tube when a salpingectomy is performed for a tubal pregnancy.

Conditions for Tubal Surgery

As I said twenty years ago, the following conditions should be present before plastic operations on the tubes are performed. The patient must be in the childbearing period, preferably less than 35 years of age. She must have at least one functioning ovary. Both tubes or the only remaining tube must be proved to be closed. There must be no other cause for the sterility but tubal

closure. There must be no tuberculous infection in the genital tract. The patient must be a good surgical risk. Of course, the husband must be fertile and healthy.

Sometimes a plastic tubal operation is justified for the effect the operation will have on the patient's morale. There are women who later in life express their gratitude for such an operation even though they never have a baby because they have a persistent hope that pregnancy is possible. The latter thought eliminates considerable stress in their married life.

Nonsurgical Therapy of Occluded Tubes

It is interesting to compare the results of nonsurgical treatment of closed tubes with those of surgery. Some patients became pregnant following a tubal patency test which apparently showed tubal closure. Most likely in the majority of these women there was a tubal spasm which prevented the escape of gas from the uterus into the tubes. In most women, however, anatomic closure can be proved either by repeated Rubin tests or by hysterosalpingography. A few gynecologists have tried to overcome tubal blockage by repeated tubal patency tests and other medical aids such as diathermy. How do the results of such conservative treatment compare with surgery?

Buxton and Southam observed 5 pregnancies (7.46 per cent) in 67 women with closed tubes who were not operated on, in contrast to only 2 pregnancies (5.6 per cent) after 35 tubal plastic operations.

Zanartu and Hamblen overcame bilateral tubal obstruction in 150 (72.8 per cent) of 206 women by means of single or repeated hysterosalpingograms. The authors considered 62 pregnancies (41.3 per cent) among the 150 women to be directly related to the relief of tubal obstruction by the hysterosalpingograms.

Grant and Mackey treated 124 women who had blocked tubes by pressure injections, gas, and iodized oil. They used a pressure of more than 300 mm. of carbon dioxide. In 53 women tubal patency resulted and there were 23, or 18.5 per cent, pregnancies among the 124 patients. At the time of their report 3 of these 23 gestations had ended in miscarriage and 2 (8.7 per cent) in ectopic pregnancies. Grant wrote me that, as of March, 1955, 300 women with blocked tubes had been treated by pressure injections at 300 mm. Patency occurred in 148 and 49, or 16.3 per cent, of the 300 women became pregnant. Among the 49 pregnancies there were 3, or 6.1 per cent, ectopic pregnancies.

Murray and Paradelo treated 47 sterile women who had tubal obstruction by nonsurgical procedures and 11, or 23.4 per cent, of these women became pregnant and 1, or 9 per cent, had a tubal pregnancy.

Arenas and Bettinotti likewise used conservative procedures in 131 sterile women with closed tubes. Following this treatment there were 22 pregnancies of which 19, or 14.5 per cent, were credited exclusively to the medical therapy.

Kurzrok and Streim gave cortisone to 8 women with nonpatent tubes, after which 5, or 62.5 per cent, of them became pregnant.

From the foregoing reports it is apparent that the results of nonsurgical treatment of occluded Fallopian tubes are not too inferior to those following surgery. It is also apparent that tinkering with closed tubes even by nonsurgical procedures, such as repeated Rubin tests under high pressure and hysterosalpingography, may lead to an increased frequency of tubal pregnancies.

The Future of Plastic Tubal Operations

I, personally, am pleased that gynecologists in different parts of the world are attempting to improve the results of plastic tubal surgery because the article I wrote in 1936 was most pessimistic. In spite of the considerable time,

effort, and ingenuity put into the improved techniques, the incidence of live babies, in my opinion, is still too low. These experimental studies should be continued and extended. Undoubtedly techniques will be developed which will enable about 50 per cent of women to conceive in the uterus after such operations, thus making these operations definitely worth while. Meanwhile, I make a plea that all candidates for plastic tubal operations be referred to gynecologists studying this problem, who have perfected special techniques, and who are using tiny instruments, fine suture material, polyethylene tubing, and other aids to improve the results. This is in line with my belief that all women who require special types of therapy, such as radiation treatment for malignant disease, radical hysterectomy for carcinoma of the cervix, exenteration operations, operations for cancer of the vulva, urinary fistulas, pseudohermaphrodism, and other afflictions which demand special skill should be sent to surgeons who now possess the necessary skill, experience, and physical stamina. Also necessary for this type of surgery are trained assistants for perfect teamwork and proper care of these patients, immediate availability of large amounts of blood for transfusion, and expert anesthetists. God speed the day when all residents in gynecology will receive the necessary training to enable them not only to carry out these operations but also to accomplish much more.

Conclusions

In 1936 an extremely pessimistic article of mine dealt with plastic operations on the Fallopian tubes. In this article the results of 818 plastic tubal operations performed by specialists in gynecology in the United States were reviewed. The results were very poor.

Are the results of the last twenty or even the last ten years much better? I have collected statistics from many men especially interested in this subject not only in the United States but also in many other countries. Data on a total of 2,113 plastic tubal operations were assembled, following which there were 405 pregnancies, an incidence of 19.1 per cent, or 1 pregnancy following every 5 operations. There were only 313 living children, an incidence of 77.3 per cent of the pregnancies, and a frequency of 15.1 per cent of all the operations, or 1 living child after every 6½ operations. The presence or absence of ectopic pregnancies was specified in 286 pregnancies, 70.6 per cent of the pregnancies. In this group there were 45 tubal pregnancies, an incidence of 15.7 per cent, or 1 ectopic pregnancy after approximately every 6 operations. If we assume there were no ectopic pregnancies in the remainder of the cases, the incidence of ectopic gestation is 11.1 per cent.

While the results are far better than they were twenty years ago, in my opinion they are still far short of what they should be to justify indiscriminate plastic tubal operations. Furthermore, a high incidence of tubal pregnancies follows these operations. Also, we must admit that the results of nonsurgical treatment of closed tubes yields results which are almost as good as those of surgery. I believe that candidates for tubal plastic operations should be sent only to those gynecologists who are at present interested in this subject and are

performing skillful operations, because the results of these investigators, while still not what they should be, are considerably better than those obtained by surgeons who perform plastic tubal operations only occasionally.

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CULDOSCOPY FOR DIAGNOSIS IN INFERTILITY

Report of 492 Cases

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DECKER'S modification of peritoneoscopy and of the way to use it for inspection of the pelvic organs has facilitated detection of occlusive, undiagnosable intrapelvic conditions that impede conception. We have used this procedure to detect such hidden obstructions and to appraise the ovaries in cases of infertility with ovulatory failure.

Material

There were 492 culdoscopies for investigation of infertility performed at the Free Hospital for Women during the ten-year period ending July, 1955. All of the procedures were done by three individuals. Approximately 80 per cent of these were performed on private patients, and the remaining 20 per cent on clinic patients.

Indications.—Culdoscopy is not considered to be a part of diagnostic routine. Indications were as follows: (1) failure of the usual diagnostic tests to disclose a satisfactory cause for long-standing infertility; (2) a suspicion of periadnexal adhesions based on history, bimanual pelvic examination, tubal insufflation (with delayed shoulder pain) or hysterosalpingogram with atypical dispersal of the opaque medium; (3) ovulatory failure as in amenorrhea, or as suggested by temperature charts and endometrial biopsies.

Method

Each patient is hospitalized for the examination and for the following 24 hours. The procedure, so well described by Decker,[1] is done under sterile conditions in the operating room. The patient is well supported in the knee-chest position, with her head, projecting beyond the table, resting comfortably on a cushion of adjustable height.

The types of anesthesia are listed in Table II. In 56.1 per cent of the cases local anesthesia was used. Novocain (2 per cent) was injected: sometimes in the vaginal epithelium, sometimes between it and the peritoneum, and sometimes into the pelvic cavity. None of these methods was satisfactory, even when combined with infiltration of the uterosacral ligaments. Spinal or epidural (rarely Pentothal) anesthesia was used in 171 cases and Pentothal intravenously, in 12, because combined procedures were planned, such as culdoscopy and curettage. No morbidity or mortality was attributable to anesthesia. In most instances examination was preceded by sedation, often with barbiturates in conjunction with chlorpromazine. It is to be noted that 33 of the patients had no anesthesia, which left much to be desired.

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In the vast majority of cases pneumoperitoneum was established with carbon dioxide to avoid prolonged shoulder pain from slow absorption of retained air.

Upon termination of culdoscopy most of the gas was expressed by manual pressure on the abdomen before withdrawal of the cannula. The patient was then placed in lithotomy position and the puncture wound in the vaginal wall closed with one or two catgut sutures.

Results

Failures.—Of the 492 culdoscopies attempted (Table I), 417, or 84.8 per cent, were successful and 75, or 15.2 per cent, were not. Therefore, despite an attempt to avoid cases with adherent, retroflexed uteri or fixed masses in the cul-de-sac, approximately one in six endeavors to enter the pelvic cavity was unsuccessful. These failures were distributed equally throughout the ten-year period, demonstrating that prolonged experience with the culdoscope did not insure the individual operator against failure. Many factors were involved, such as operative conditions, quality of assistance, local anatomy, as well as temperament of the patient and degree of anesthesia. Separation of peritoneum from vaginal epithelium by the infiltration of Novocain solution was also considered a contributory cause of failure.

It is interesting to note that, of the 75 failures, 32 had subsequent laparotomy which disclosed significant pathologic conditions in the cul-de-sac in 23, or 72 per cent.

TABLE I. CULDOSCOPIES ATTEMPTED

	NO.	%
Successful	417	84.8
Failed	75	15.2
Total	492	

TABLE II. TYPE OF ANESTHESIA

	NO.	%
Local Novocain	276	56.1
Spinal	158	32.1
Epidural	13	2.6
Pentothal (intravenous)	12	2.4
None	33	6.7
	492	

Culdoscopic Diagnosis.—Preculdoscopic impressions were usually confirmed at examination (Table III). In 88 per cent of 50 women who were thought to be anovulatory, no evidence of rupture of follicles was seen; in the others new or old stigmas were present. Diagnoses of generalized pelvic adhesions were supported in 77.7 per cent of 121 cases.

TABLE III. CULDOSCOPIC DIAGNOSIS

PRECULDOSCOPIC IMPRESSIONS		CULDOSCOPIC DIAGNOSIS	% ACCURACY
Dysfunctional ovaries	50	44	88.0
Pelvic adhesions	121	94	77.7
Normal	246	162	65.9

As previously noted, one indication for culdoscopy was the apparent normality of the whole mating which was nevertheless infertile. In 246 such

cases, explanatory pelvic pathologic conditions were unexpectedly found in 84, or 34.1 per cent.

Laparotomy was performed on 135 patients previously culdoscoped; in these, findings were confirmed in 99.2 per cent. Additional pelvic pathology not observed with telescopic aid was infrequent and usually consisted of minor endometriotic implants over the bladder and anterior surface of the uterine fundus.

Analysis of Findings.—Culdoscopy was important not only when it revealed pathologic conditions, but also when all was normal. The findings are listed in Table IV. No pathology was found in 103 patients and negligible pathology in 92. The latter included such conditions as seedling fibroids, endometriotic implants, and tuboovarian adhesions thought to be incapable of interfering with conception. Only one out of every four infertility patients had a completely "normal" pelvis at culdoscopy.

TABLE IV. CULDOSCOPIC FINDINGS

	NO.	%
Normal	103	24.7
Negligible sterility pathology	92	22.1
Fertility-impeding pathology (222 patients)		
Tuboovarian adhesions	143	34.3
Stein-Leventhal ovaries	45	10.8
Hypoplastic or atrophic ovaries	34	8.1
Total	417	

Of the 417 successful culdoscopies, pathology thought to be interfering with or preventing conception was found in 222, or 53.2 per cent. There were 143 patients with significant tuboovarian adhesions (Table V). General or localized adhesions following appendicitis, previous operation, puerperal sepsis, septic abortions, or bacterial salpingitis other than tuberculosis were found in 104 patients. Of those remaining, 34 women had endometriosis and 5 had adhesions from tuberculosis.

TABLE V. CAUSES OF TUBOOVARIAN ADHESIONS

	NO.	%
Peritonitis	104	72.7
Endometriosis	34	23.8
Tuberculosis	5	3.5
Total	143	

Bilateral ovarian pathology was noted in 79 cases. There were Stein-Leventhal type ovaries in 45, and in 34 the ovaries were hypoplastic or atrophic.

Results of Surgical Treatment.—It is interesting to note the pregnancy rate in those patients who accepted advised surgery following culdoscopic diagnosis and in those who did not (Table VI). Of the 222 patients who had significant pathology, surgery was recommended to 176. Of these, 135 complied and 38, or 28.1 per cent, conceived following operation. In the 41 patients not operated upon, pregnancy occurred in 6, or 14.6 per cent. Thus, in our experience, chances of pregnancy are doubled in those patients who accept a recommendation of surgery based on culdoscopic diagnosis of pathologic conditions causing infertility.

Disadvantages.—No death or febrile morbidity was encountered. There were complications in 6 cases. Rectal perforation occurred in one case. This

patient was followed with bed rest only; the perforation closed spontaneously and no trouble ensued. Although rectal damage was suspected in 4 other patients, proctoscopy was negative and no morbidity occurred. Following culdoscopy, bleeding from the puncture site occurred in 3 cases early in the series and in one case the omentum prolapsed through it. These two early complications prompted the present practice of closing the wound with one or two sutures. Postculdoscopy emphysema as reported by Fortier[2] and by Herman and De Pietro[3] was encountered in one case without complications.

TABLE VI. RESULTS IN CASES IN WHICH OPERATION WAS ADVISED

		SUBSEQUENT PREGNANCY	
		NO.	%
Accepted surgery	135	38	28.1
Refused surgery	41	6	14.6
Advised surgery	176	44	25.0

Comment

In the evaluation and treatment of a barren patient any diagnostic aid which helps to affix the cause or causes of infertility is of obvious importance. The advantages of culdoscopy in general gynecologic diagnosis have been amply reviewed elsewhere.[3-8] The failure rate is high.[9, 10] The auxiliary visualization of tubal patency with the use of indigo carmine, methylene blue, or penicillin solutions washed through the uterus and tubes at the time of culdoscopy has been used freely by others[11] with good results. The mechanical treatment of tubal occlusion by insufflation under high pressures during culdoscopy is discussed by Decker[12] but is not yet considered of value in our clinic. In the evaluation of adnexal pathology interfering with tubal reception of the egg, culdoscopy is exceedingly important.

As was noted, a little over one-half of the patients with unexplained infertility were found to have definitive pathologic conditions capable of interfering with normal reproduction. Possibly many of the 195 patients found to have normal pelvic anatomy would have undergone futile exploratory laparotomy without the screening diagnostic help of the culdoscope.

When laparotomy is contemplated, it behooves the investigator to utilize all the adjuvants at his command. We believe that a culdoscopic examination of the pelvis is highly desirable when, in the absence of definitive indications, surgery is considered. Visualization is rarely necessary for such conditions as closure of the fimbriae detected by x-ray, generalized adhesions previously found at laparotomy, history of bilateral tubal ligation, a palpable ovarian tumor, or significant myomas. Culdoscopy is also of great value when more standard investigative procedures have failed to explain inability to conceive.

Summary

1. An analysis of 492 culdoscopies done for the diagnosis of sterility at the Free Hospital for Women in the ten-year period ending July, 1955, has been presented.

2. Of the attempted culdoscopies, 417, or 84.8 per cent, were successful and 75, or 15.2 per cent, failed.

3. When an attempted culdoscopy fails, the chances are about three out of four that an exploratory laparotomy will disclose pelvic pathology which explains the failure of penetration of the cul-de-sac.

4. Novocain infiltration, now considered unsatisfactory, was the most common form of anesthesia, being used in 276 cases, or 56.1 per cent. The second in frequency was spinal, used in 158 cases, or 32.1 per cent. Other types included epidural Novocain and intravenous Pentothal. In 33 cases, no anesthesia was given.

5. Culdoscopy showed the cause of sterility by revealing unexpected pathology in 34.1 per cent of patients thought to be "normal."

6. Pelvic pathologic conditions interfering with reproduction were found in 222, or 53.2 per cent, of the 417 successful culdoscopies.

7. The chance of pregnancy appears to be doubled if the culdoscope-screened patient with pathology undergoes proper surgery.

We are indebted to Dr. William J. Mulligan for permission to include his 86 cases, and to Dr. Herbert W. Horne, Jr., for his 68.

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PRELIMINARY REPORT ON THE USE OF ILEUM AS OVIDUCT IN THE DOG*

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(From the Department of Obstetrics and Gynecology and the Harrison Department of Surgical Research of the University of Pennsylvania)

RECENT surveys[23, 27] show that 30 per cent of infertile women have occluded Fallopian tubes. To restore these oviducts gynecologists have carried out many different procedures.[4, 8, 12, 16, 18, 19, 21] These include linear salpingostomy, reconstruction and reimplantation of the oviducts over catheters and tubing of various materials, some native to the patient, such as arteries and veins, others foreign, such as allantoic membrane and polyethylene tube. These operative procedures give a fair rate of anatomic patency but a low incidence of pregnancy.[6, 13, 14, 21, 24] One might infer that the operative procedure did not restore the physiologic function. This altered physiologic integrity may be concerned with the reception, fertilization, or transportation of the ovum. The following is a preliminary report of an attempt to replace an oviduct system with an isolated intact segment of terminal ileum.

Method

Healthy female nonpregnant mongrel dogs that weighed from 10 to 20 kilograms were used. Preoperative preparation included oral Terramycin for three days and a liquid diet for twenty-four hours. The animal was anesthetized with intravenous Nembutal sodium, its abdomen was prepared with iodine, and the peritoneal cavity was entered through a midline incision. A segment of terminal ileum containing an arcade of vessels was isolated from the gastrointestinal tract with care to maintain its blood and nerve supply. The continuity of the ileum was restored in the usual manner of intestinal anastomosis. The defect in the mesentery was closed up to the origin of the arcade of vessels which supplied the isolated segment. The segment of ileum was then irrigated with saline (Fig. 1).

The left horn of the uterus was located and followed to the uteroovarian ligament, where the ovarian bursa was identified. The ligament and oviduct were divided and ligated. The bursa was opened at the site of the abdominal ostium to expose the ovary (Fig. 2). The proximal end of the isolated loop of ileum was then sutured to the periphery of the opening in the ovarian bursa. This maneuver obliterates the Fallopian tube, and exposes the ovulating surface of the ovary to the lumen of the ileum. The omentum was brought down to cover the line of anastomosis between the ileum and ovarian bursa. Then an end-to-end or an end-to-side anastomosis between the distal end of the ileum and the left uterine horn was performed. The right uterine horn was then divided and ligated at the uteroovarian ligament (Fig. 3).

*Presented at a meeting of the Obstetrical Society of Philadelphia, May 5, 1955.

Postoperatively the dog received intravenous fluid, vitamins, and antibiotics. She was given oral fluids and food as tolerated after the fourth postoperative day.

Results

Twelve dogs were operated upon. Two dogs died in the immediate postoperative period from intussusception, one of the jejunum and the other of the

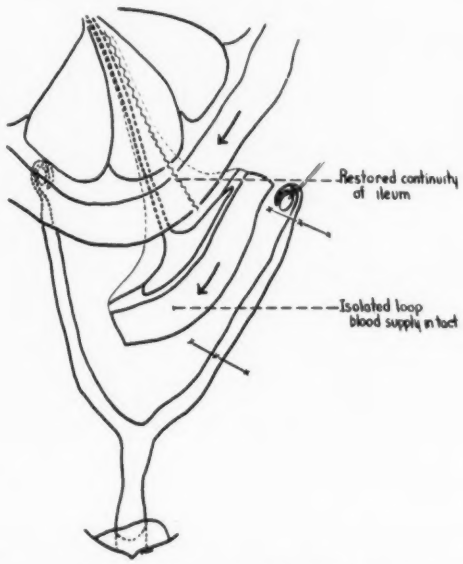

Fig. 1.—Line drawing showing canine genital tract, isolated intact segment of ileum, and reconstructed gastrointestinal tract.

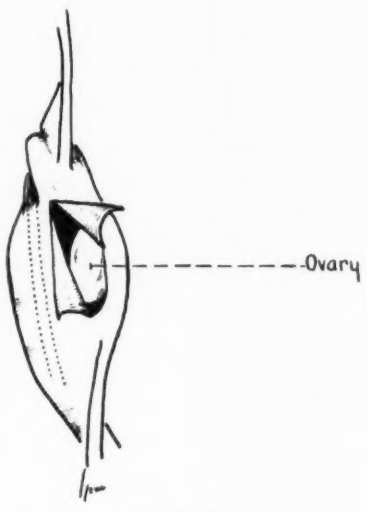

Fig. 2.

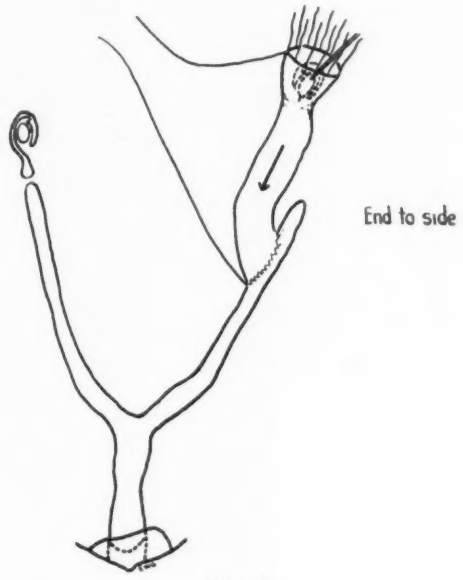

Fig. 3.

Fig. 2.—Line drawing showing the ovarian bursa opened to expose the ovary.

Fig. 3.—Line drawing showing the completed operation with ovary suspended in the ileum, distal segment of ileum anastomosed to the left uterine horn, and sterilization of the right uterine horn.

Fig. 4.—Photograph of specimen No. 476, showing the isolated ileal segment with its mesentery. Both ovarian bursae have been opened to expose the ovaries.

Fig. 5.—Hysterogram of specimen No. 476, two and one-half months after ileal-uterine anastomosis, showing patency with narrowing at the anatomic site, and the diameter of the ileal segment approximating that of the normal uterine horn.

ileum. Ten dogs survived the operation. One dog was stolen, 3 died of intercurrent disease, 2 were sacrificed, and at present 4 are living and well.

Two dogs were sacrificed, one (No. 476) at 2½ months and the other (No. 1352) at 7½ months. In both animals the genital tract and segment of ileum appeared unchanged except for a decrease in the diameter of the ileum to approach that of the uterine horn (Fig. 4). A hysterogram made on the specimen of dog No. 476 demonstrated roentgenologic patency with definite narrowing at the site of anastomosis of the ileum and uterine horn (Fig. 5). Microscopic sections of the ovaries, ileum, and uterine horns (Fig. 6) were reviewed by Dr. John McGrath, Associate Professor of Veterinary Pathology, University of Pennsylvania, who reported them as being normal. The ovary exhibited many follicles in various stages of development with no evidence of acute or chronic inflammation. The ileum showed a decrease in the thickness of the villi, and an increase in the compactness of the muscle layers. The endometrium was in a typical phase of anestrus with no evidence of inflammation.

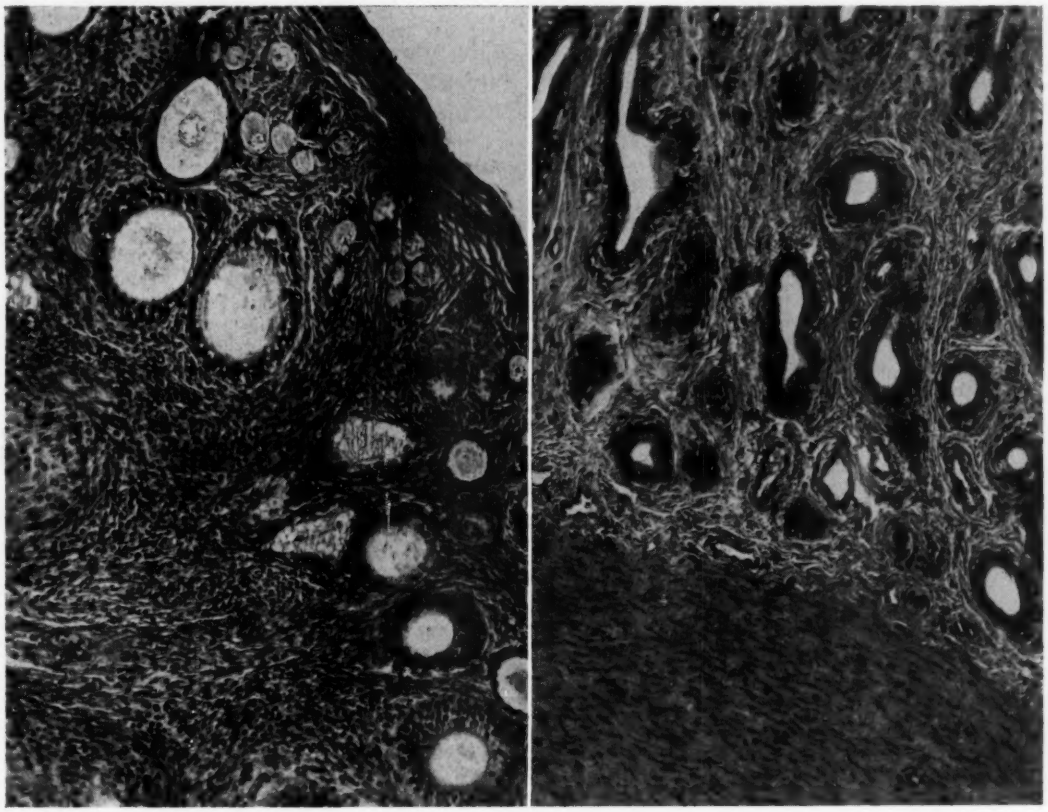

Fig. 6.—Microscopic sections (specimen No. 1352) of left ovary and uterine horn seven and one-half months after the ileum was implanted as oviduct. Note the normal-appearing follicles, endometrial glands, and lack of stromal reaction. (×200; reduced ⅓.)

Comment

A brief comparison of the Fallopian tube and ileum shows many anatomic similarities. Each has a serosal surface, arcade blood supply, longitudinal and circular muscle layers, sympathetic and parasympathetic innervation, and a folded vascular mucous membrane of columnar epithelium. The ileal epithelium presents a brush border while that of the tube is ciliated.

Although ciliary activity may be concerned in aiding the passage of the ovum, peristalsis is now generally thought to be paramount.[5,15,29] Ileal and Fallopian tube peristalsis[9,10] occurs at the rate of six to ten times per minute. Several recent experimental and clinical studies[1-4,7,11,20,22] have shown that an isolated ileal segment exhibits peristalsis and can adequately replace a damaged ureter. We have seen peristalsis in the ileal segment after its implantation as an oviduct. The segment should be able to transport an ovum[15,17] which measures 120 to 200 microns since it can readily carry carbon particles of smaller size.

Recent reports[25,26] suggest that tubal secretions may be essential for fertilization of the ovum. The lack of these secretions in the ileal segment or the presence of the ileal secretions may prevent fertilization or transportation of the ovum. Our investigation shows that the ovary, ileum, and endometrium apparently are unharmed by the procedure. It is known that follicular fluid is alkaline, that sperm survive best in an alkaline medium, and that the pH of the ileum is 7.16 to 7.38.[28] We have set up experiments to see if the secretions of the ileum have any ovicidal or spermicidal properties.

Conclusions

1. The dog can survive the isolation of a segment of terminal ileum with its implantation into the genital tract as replacement for the oviduct.

2. The ovary, ileum, and uterine horn apparently are unharmed by this procedure.

3. As yet we have not attempted to mate these animals. We plan to increase our colony of dogs with ileum for oviduct and do plan to mate them.

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Discussion

DR. S. LEON ISRAEL.—It is now common knowledge that latter-day tuboplastic surgery, even though creating patent tubes, does not result in more than half as many pregnancies. It is widely appreciated that a new dramatic approach to the problem is required. Drs. Kucharczuk and Greene have successfully mastered an original technique of tubal replacement in the dog. Applying a principle previously shown to be effective in substituting a segment of ileum for an organ such as the bladder and for a passageway such as the ureter, they have demonstrated that it is possible to link a resected uterine horn to the ovarian bursa by means of a viable loop of transplanted ileum. This, the preliminary phase of their problem, they have settled. They are as curious as we to observe whether or not such a transplant will function as a proper tube.

The authors, intent now upon their mating colony of gut-tubed dogs, are not yet ready to discuss the possible application of their technique to the human female. We, however, cannot refrain from doing so. What does such anticipation envisage? We must picture two sets of hurdles to be jumped—one, surgical, and the other, physiologic. It will not be so easy to preserve the mesenteric arcade of blood vessels for an ileal transplant in the woman as in the bitch. Nor will it be so simple to implant the relatively wide, but compressible, ileal segment into the firmly muscular uterine cornu, as it is to anastomose ileum and uterine horn.

Granting for the moment that these surgical obstacles can be overcome, how shall we face the physiologic ones? In lesser mammals, such as the dog, ova are discharged into a closed space, the ovarian bursa, and enter the oviduct with relative ease. In the human, there is no bursa. Ovulation occurs through a fissure in the surface of the ovary, and the ovum, being carried to freedom by the current of follicular fluid, floats away from the tubal opening because of gravity. We are forced to conjecture that tubal motion, arising in part from the extratubal muscles of Rouget, salvages the freshly liberated ovum. This act of tubal grace is probably made possible by a vacuum cleaner-like suction created by both cilial action and segmental contractions. With the ovum safely ensconsced within its infundibulum, the Fallopian tube must now serve as a passageway to both outward-bound sperm and inward-directed conceptus. But is it merely a passageway, one in which segmental contractions of an ileal loop could replace those of the tube? Or, as the authors themselves suggest, do the secretory elements of tubal epithelium contribute significantly to the welfare of the passing conceptus? According to the investigations of Joel, cytoplasmic tubal secretion is rich in both glycogen and ascorbic acid. It has not yet been proved, however, that such secretion is necessary to either spermatozoon or ovum.

If the experiments of Drs. Kucharczuk and Greene, the report of which we have been privileged to hear for the first time, succeed—if their animals yield litters—they will have proved much. Certainly, it will become apparent that intestinal motility can replace the tubal variety. If, to whet further their experimental palates, a single human pregnancy is achieved through a tube of intestinal origin, they will have established the fact that the tube-borne conceptus can do without the alleged pabulum derived from the endosalpinx.

INDICATIONS FOR HYSTERECTOMY*

A Panel Discussion

MODERATOR: CHARLES MCLANE, M.D., NEW YORK, N. Y.
PANELISTS: NORMAN F. MILLER, M.D., ANN ARBOR, MICH.
RICHARD W. TE LINDE, M.D., BALTIMORE, MD.
ALBERT H. ALDRIDGE, M.D., NEW YORK, N. Y.

Carcinoma of the Endometrium and of the Ovaries

DR. NORMAN MILLER.—At the beginning of this century hysterectomy was the treatment of choice for carcinoma of the endometrium. Indeed, it was at first the only treatment. About 1925 the idea developed that preliminary irradiation might be of value. There were very good reasons for considering such preliminary therapy. While the operation was successful, the follow-ups, which were few and far between, indicated that the patient didn't always survive very long. There were recurrences, locally. There were manipulative spread and metastases to the chest and other parts of the body and it was felt that perhaps by irradiation prior to operation these hazards could be reduced. I believe they were reduced. But like everything else, I think the carcinoma of the endometrium situation has changed.

Back in those early days carcinoma of the endometrium was in an advanced state when diagnosed. Today we find the diagnosis being made much earlier and I admit that there are many patients today who probably do not need either preoperative x-radiation or preoperative radium irradiation. But I believe these patients should be individualized. I am firmly convinced that there is no treatment at this time better than irradiation followed by surgery for carcinoma of the endometrium. I am familiar with the figures that the Radiumhemmet has reported, which I believe are the best in the world for irradiation alone in the treatment of carcinoma of the endometrium. They do not equal those for surgery combined with preoperative radiation.

In so far as carcinoma of the ovary is concerned, again we have gone through a cycle There was a time when the only treatment was operation and removal of all the pelvic organs. Then we came to the stage where we considered leaving the uterus so that intracavitary irradiation of the pelvis might be considered along with external irradiation in the hope that the results could be improved. Now most gynecologists have discontinued leaving the uterus for the simple reason that the figures did not show improved results when the uterus was left in. Indeed there are very good reasons why the uterus should be removed. I believe you are familiar with the fact that, in carcinoma of the ovary, involvement of the uterus and the tubes is not uncommon. In some recent studies that have been made, where cytological investigation was carried out, free carcinoma cells were found in the tubes and in the uterine cavity. So I believe that for carcinoma of the ovary we have in the operable cases a clear-cut indication for doing a hysterectomy.

In our treatment of carcinoma of the endometrium, we generally supplement or precede the hysterectomy with x-irradiation but I believe there is room

*Presented at a meeting of the New York Obstetrical Society, March 8, 1955.

for individualization of patients, principally because many of these patients are reporting for treatment in an earlier stage of the disease. In so far as cancer of the ovary is concerned this is still a real problem as you all know. The major aspect of this problem is not what to take out but how to diagnose it early.

Perhaps the discovery that loose cells from ovarian carcinoma may be recovered from the uterus will be a small step leading to earlier diagnosis, which is perhaps the most important factor in obtaining improved results in the management of carcinoma of the ovary.

Carcinoma of the Cervix

DR. RICHARD TE LINDE.—I like to think of the treatment of carcinoma of the cervix historically because, I do date back to the previous era when the Wertheim operation was done. I did several of these operations during my residency. By the Wertheim operation I mean the radical operation, doing a salpingo-oophorectomy removing a good part of the upper portion of the vagina, and a pelvic lymphadenectomy.

There have been some disputes as to just what the Wertheim operation is. As a matter of fact, Wertheim did not always perform the same operation, so there is no wonder there is confusion. In the later years he decided lymph gland dissection was of very little value and many of the operations which he did were of the type we now call a modified Wertheim operation and we use it for carcinoma in situ without lymphadenectomy.

At the turn of the century Dr. Cullen wrote his cancer book and reported a 26 per cent five-year salvage in the cases operated upon at the Hopkins Hospital. Then came irradiation and, very grudgingly, these cases were passed to the radiologist. The earlier cases in particular were turned over with reluctance.

With radiation there occurred considerable improvement in results in even the advanced cases, so that about 15 years ago or so the figure from the better clinics for five-year salvage stood at about 26 per cent. Now this is the same figure that Dr. Cullen reported but these figures are not comparable. Dr. Cullen's salvage was 26 per cent of the cases operated upon. The 26 per cent of the radiologist was 26 per cent salvage of all the cases seen. So obviously the results at that time were very much better with irradiation. Irradiation has continued to improve in its technique and has yielded improved results so that our last year's figure was 47 per cent salvage for Stages I, II, III, and IV. If we throw in 8 cases of carcinoma in situ that we had that year, our salvage is up to 53 per cent.

There is one man who stuck to the Wertheim type of operation all of his life and I know you are all familiar with the work of Victor Bonney. His last report was on 600 cases that he had personally operated upon. He operated upon 63 per cent of the patients that he saw and his salvage was 40 per cent of the patients operated upon. Now if you multiply 40 by 63 you get 25.2. In other words you get practically the same figure that had been attained with irradiation about 15 years ago. About the time that Bonney stopped his active career, however, he still had a 14 per cent mortality and a great many fistulas, whereas with irradiation in those days the mortality was 1 or 2 per cent.

Then came Dr. Meigs' much-needed experiment, which he began in 1939. He selected his cases very carefully and at first took only Stage I cases and a few selected early Stage II cases in thin women, who were good operative risks and under 50 years of age. Not long ago he published his five-year salvage which is 85 per cent for Stage I. How does that compare with the salvage with irradiation? Our five-year salvage in Stage I for the year 1948 was 84

per cent. In other words, the figures were practically identical for that year but Meigs' cases were selected and ours were the run of the mill. The thin woman, the young woman, the good operative risk is also a better irradiation risk.

I think I ought to say just one word about the Schauta operation—the radical vaginal hysterectomy. Professor van Bouwdijk Bastiaanse of Amsterdam is one of the chief advocates of that today. In Stage I his five-year salvage is 59 per cent which is considerably lower than the salvage from many of the better irradiation clinics in that group of cases. The operation does not appeal to me although Dr. Van Bouwdijk Bastiaanse is a master of it technically. I believe that that operation has little if any place in the treatment of carcinoma of the cervix.

There has been only one controlled study on the relative value of surgical and radioactive technique that I know of. This was done right here in the City of New York by Dr. Howard Taylor and Dr. Twombly in which alternate cases of Stages I and II were operated on and irradiated. What were their five-year results? The salvage in the cases operated upon was 60 per cent and the salvage in the irradiated cases was 68 per cent. So there was a little edge in favor of irradiation. I think almost everybody believes that Stages III and IV should be treated with irradiation.

After looking over these figures and trying as hard as I can to compare one set of figures with another, this is my present belief regarding the treatment of cervical cancer: In Stage 0 intraepithelial carcinoma we do the modified Wertheim operation. This operation is a total hysterectomy but we take a couple of centimeters of parametrium on either side, and catheterize the ureters preoperatively so as to know where they are all the time and thus avoid dissecting them out with resulting fistula formation. We also take about a 2 cm. cuff of vagina. We have been accused of being too radical in treating carcinoma in situ by hysterectomy. I feel nothing short of this surgery should be done provided you are very sure you are dealing with a bona fide case of carcinoma in situ because you never know just how extensive that lesion is until you have the whole specimen to examine. We have many cases in which the lesion extends as high as the internal os and if we had done an amputation of the cervix in many cases we would have left carcinoma in. In fact, we have one case in which the "in situ" replaces the endometrium and goes way up to the fundus of the uterus where it becomes invasive. The reason I think a vaginal cuff should be taken—and I think that is the most important deviation from the normal hysterectomy in dealing with carcinoma in situ—is that although the lesion is superficial it is many times very extensive on the surface of the cervix. We have had one case in which the lesion was found on the cervix and also out in the vaginal vault. You probably all know that Dr. Meigs has reported three cases of recurrence in the vaginal vault after hysterectomy and I am sure his hysterectomy is fully as radical as ours is. We have had no recurrence in the vaginal vault in our in situ cases.

If you look at the figures on surgery done by the few experts and those on irradiation, the results are just about the same in Stage I. Before a man undertakes the Wertheim operation for Stage I carcinoma of the cervix he should look himself in the eye and ask himself, "Have I any right to operate on this woman with my operative experience when I can get just as good results by irradiation?" Avoiding surgery will certainly decrease the chances of ureteral injuries which even the best operators have. In fact, I think some of the best operators, who do the most thorough job, have the most ureteral-vaginal fistulas. The more thorough the job of eradicating the cancer, perhaps the more fistulas you will have.

As far as Stages II, III, and IV are concerned, in our clinic we feel they should be treated by complete irradiation.

Benign Conditions of the Uterus or Adnexa

DR. ALBERT H. ALDRIDGE.—Hysterectomy by either the abdominal or vaginal route is now the treatment of choice for a variety of benign gynecological conditions. Within the past few years the risks of these operative procedures have been reduced to a low level by (1) improved surgical techniques, (2) better anesthesia, (3) modern routines to prepare patients for operation, (4) facilities for adequate replacement of blood loss, and (5) development of effective means to prevent and to treat infections. This has led to modifications in indications for hysterectomy and to an increase in the percentage of complete hysterectomies which until recent years were considered by some gynecologists to be unnecessarily radical.

Gynecologists have accepted the advantages of complete hysterectomy whenever there are indications to remove the uterine corpus. They are convinced that the results of hysterectomy are on the whole better than those from irradiation therapy. Partial hysterectomy and irradiation therapy are now reserved for a few patients who are poor surgical risks and for those in whom unusual technical problems are encountered. The incidence of vaginal hysterectomy has increased in all gynecological clinics.

Many women who consult a gynecologist have symptoms and conditions which constitute definite and acceptable indications for this procedure. Others have troublesome symptoms which can be promptly and positively relieved by hysterectomy but they have little evidence of any abnormalities of the pelvic organs. Their symptoms may or may not respond to more conservative therapeutic or surgical procedures. Some have had prolonged treatment before they consult a gynecologist. They are anxious for prompt and permanent relief from their symptoms. In these days, many patients need assurance that they do not have cancer and that the treatment which is recommended will prevent development of pelvic cancer in the future.

The decision as to whether a woman's uterus should be removed must be based not only upon her symptoms and the condition of her pelvic organs but also upon her age, marital status, and the importance of retaining her menstrual and childbearing functions.

Hysterectomy is indicated for the following benign pelvic conditions in women at or near the menopause and for those who have conditions which cannot be adequately treated by more conservative methods:

1. *Uterine fibromyomas,* which show signs and symptoms of active growth or degeneration and those which cause excessive uterine bleeding and/or symptoms of pressure on the pelvic structures. This includes regrowth of fibroids after previous myomectomy.
2. *Uterine adenomyosis* which is diffuse and extensive enough to cause pelvic pain, abnormal uterine bleeding, and severe dysmenorrhea.
3. *Uterine fibrosis and vascular sclerosis* which produce physical changes in the uterine musculature and symptoms which are difficult to differentiate before operation from those due to adenomyosis. In fact both conditions are found frequently in the same uterus. I realize that there is a difference of opinion regarding *uterine fibrosis* and *vascular sclerosis,* that is, whether there are such conditions. At the Woman's Hospital we have accepted these diagnoses which are made by our Pathologist, Dr. Leon Motyloff, who was trained by the late Professor Robert Meyer and has had much experience in gynecological pathology.

4. *Endometriosis* which is extensive enough to necessitate removal of both tubes and ovaries for relief of pelvic symptoms.

5. *Pelvic inflammatory disease including pelvic tuberculosis* which has failed to respond to palliative therapy and is extensive enough to necessitate removal of both tubes and ovaries for relief of pelvic symptoms.

6. *Functional uterine bleeding* which cannot be controlled by a suitable hygienic routine, adequate endocrine therapy, psychotherapy, and repeated curettage of the uterus.

7. *Recurrent or persistent uterine bleeding* after irradiation therapy for benign uterine conditions.

8. *Severe dysmenorrhea* which has failed to respond to all other types of treatment.

9. *Ovarian cysts or benign tumors* which necessitate complete removal of both ovaries.

10. *Uterine prolapse* if the uterus is abnormal or the prolapse is extensive or complete.

11. At times for the following obstetrical complications: (a) uncontrolled hemorrhage from uterine atony; (b) ruptured uterus; (c) premature separation of the placenta; (d) placenta accreta; (e) fibroids which are extensive and often degenerated; and (f) hydatidiform mole if tests for chorionic gonadotropin continue to be positive or if they become positive after being negative provided the uterus has been carefully and completely emptied.

Hysterectomy is contraindicated for the following benign pelvic conditions in patients for whom it is important to preserve the menstrual and/or childbearing functions and for some women who are poor surgical risks:

1. *Uterine fibromyomas* which are asymptomatic or can be adequately treated by myomectomy.

2. *Uterine adenomyosis* which is diffuse and is not causing enough symptoms to justify removal of the uterus or is localized and can be excised for relief of symptoms.

3. *Endometriosis* which requires surgery and is localized so that it can be removed or destroyed, leaving one normal tube and a part of one ovary.

4. *Pelvic inflammatory disease* which requires surgery if one functioning tube and at least a part of one ovary can be retained.

5. *Functional uterine bleeding* unless it has failed to respond to a suitable hygienic routine, adequate endocrine therapy, psychotherapy, and repeated curettage.

6. *Benign ovarian cysts and tumors* which can be resected in such a way as to leave at least a part of one ovary and a normal tube.

7. *Normal uteri* which are partially prolapsed.

8. *Sterilization of a patient* rather than by tubal ligation if the uterus is relatively normal.

Discussion

PRESIDENT MCLANE.—The rest of the program we thought we would devote to questions. The various members of this panel have had to talk up to this point on specific topics. I would like to have some questions from the floor directed to specific individuals to produce further discussion of this matter of hysterectomy.

DR. J. EDWARD HALL.—What are the indications for hysterectomy when dysmenorrhea is present? I would like Dr. Aldridge to expand a little more.

DR. ALDRIDGE.—It is assumed that Dr. Hall's question refers to dysmenorrhea in women who have relatively normal pelvic organs. In such circum-

stances menstrual pain can usually be adequately controlled or relieved by antispasmodic or pain-relieving drugs, hormone therapy, psychotherapy, and/or various gynecological procedures such as cervical dilatation, uterine curettage, operations for retroversion, and resections of the presacral nerve. Severe dysmenorrhea may or may not be relieved after childbirth. Every gynecologist knows that abnormal mental and emotional states are important factors in the causation and exaggeration of menstrual pain. Effective psychotherapy is difficult to arrange and at best fails often to produce results.

Hysterectomy during the childbearing years to relieve dysmenorrhea is rarely indicated and should never be considered until all types of therapy outlined above have been tried. If they fail, removal of the uterus in occasional cases offers the only means by which woman can be relieved of prolonged severe dysmenorrhea and can be restored to normal physical and emotional health.

Whenever a surgeon is forced to resort to hysterectomy for relief of disabling menstrual pain, he must usually acknowledge a measure of defeat in that the patient has probably not had an opportunity to get complete benefit from other types of treatment and especially from psychotherapy.

DR. CLAIR E. FOLSOME.—I was going to ask what the clinical criteria are for adenomyosis?

DR. MILLER.—I have heard several terms used here this evening which disturb me a little. One is fibrosis uteri, and I understand there is no such entity. Otto Schwarz, you may recall, studied that problem. In differential staining of these enlarged uteri, the amount of connective tissue does not appear to be excessive except in approximately 10 per cent of the patients suffering from what has been called from a clinical standpoint fibrosis uteri.

The other term that bothers me in differential diagnosis is adenomyosis uteri. It is a difficult clinical diagnosis to make in its less advanced form. The only criteria I have for making this diagnosis are two: one is abnormal bleeding or spotting and it does not have to be excessive, and the second is enlargement and firmness of the uterus. I am frank to admit that I cannot prove the diagnosis until I have the specimen.

DR. TE LINDE.—Adenomyosis of a certain degree is a common lesion. When Roger Scott and I studied our external endometriosis we went over all the cases of internal endometriosis too. We found there were just as many internal as external recorded in our laboratory but most of the cases of adenomyosis were asymptomatic and of minor degree. The major lesion of real diffuse adenomyosis of the uterus is not a very common lesion.

The diagnosis is extremely difficult to make with certainty and, frankly, I operate for the symptoms. If the patient has sufficiently excessive menstruation and if her dysmenorrhea is sufficiently bad I suspect the diagnosis and operate but sometimes I do not find it. If you combine these symptoms with a symmetrical enlargement of the uterus you have something to make one suspicious of adenomyosis.

DR. JOHN A. KELLY.—I should like to ask Dr. Te Linde what is his classification of in situ carcinoma of the cervix?

DR. TE LINDE.—I will try to answer this question as briefly as I can but I would like to have a few minutes to defend my views.

There seems to be some question as to whether Dr. Galvin and I in our original publication went overboard in talking about invasion in the 72 of 108 cases which we had. I am perfectly willing to admit that the term "invasion" was ill chosen as it was interpreted. In 72 of the 108 there was carcinoma beneath

the surface. I mean these epithelial cells which had all the characteristics of malignancy on the surface invaded glands and in some instances invaded the stroma. When it invades glands, even though those glands are way up in the endocervix, we still call it carcinoma in situ. I think there is agreement by most of the people who are working with it that they are willing still to call it carcinoma in situ, when the glands are invaded without true stromal invasion. But I agree that there have been a tremendous amount of misunderstanding and a tremendous amount of misinterpretation on the part of pathologists. Many sections that are sent to me from pathologists with a diagnosis of carcinoma in situ, have only a mild degree of what we would call basal-cell hyperactivity. According to our views there must be an involvement of the full thickness of the epithelium by these abnormal cells to justify a diagnosis of carcinoma in situ. I do not think that carcinoma in situ is invasive cancer of the cervix and we do not include these cases in our statistics of invasive cancer.

As to the matter of treatment lesser than hysterectomy, I could show you many, many sections in which if we had amputated the cervix we would have cut right through carcinoma in situ. Dr. Paul Young reports that he had 42 cases that he treated with something less than a total hysterectomy and, of those 42 cases, 14 subsequently required further treatment for carcinoma of the cervix. So I think when you are dealing with something which is potentially malignant and you have a chance to strike it, you should strike it. I do not mean that all cases of carcinoma in situ become invasive cancer but I do mean that many cases of invasive cancer are preceded by carcinoma in situ. Of 723 cases of advanced cancer that we were treating in our clinic we had biopsies from one to 19 years before on 13 cases. We went back and restudied those 13 cases. One had no epithelium. Therefore we had 12 cases with epithelium and in 11 of the 12 we found carcinoma in situ.

In the few cases in which we operate for invasive cervical cancer we do the typical Wertheim operation. We do it on the cases of Stage I and some Stage II that fail to respond to irradiation or have local recurrences in the cervix.

I did not say that I thought that Stage III's and Stage IV's were not suitable for irradiation. I say almost everyone agrees that that is the only treatment that there is for them and that we treat them that way, but I do not think they are as amenable to radiation naturally as Stages I and II.

DR. OSCAR GLASSMAN.—I would like to ask Dr. Miller about carcinoma of the endometrium. He says in some of these cases he gives radiation preoperatively. I would like to ask him whether in the cases which do not receive preoperative radiation he always gives postoperative radiation?

DR. MILLER.—We do not use postoperative radiation in cases of carcinoma of the endometrium, nor do we use irradiation either pre- or postoperatively when we operate for carcinoma of the cervix. It seems to me if we are going to learn something about how to treat some of these diseases we should not be mixing our treatments unless we have a specific and clear-cut indication for so doing.

When we use it preoperatively, as in carcinoma of the endometrium, we feel that we are accomplishing certain specific things. One, we are giving the cancer cells a good stiff jolt. We hope thereby to minimize manipulative spread at the time of operation. Second, we formerly thought that maybe we could do something to the lymphatics such as seal them off, but we have long since learned that we dilate some and seal others. We have discovered, too, that we reduced the vascularity by preoperative radiation, if we waited a reasonable length of time and we think six weeks is about right. The fourth thing we expect from preoperative irradiation in carcinoma of the endometrium

is to reduce vaginal recurrence. We think we accomplish this. The final and most important reason for preoperative irradiation of course is the improvement of the end result. We believe we do achieve better and longer survival.

In our series of cases of carcinoma of the endometrium treated by preoperative x-ray, then operation we have 87.5 per cent five-year survivals. I know there are others who report 90 per cent but some of these series are small in number. It is going to take years before we will know positively which plan is best and the question may never be answered because if we keep on diagnosing these cases earlier we may gradually discard supplemental therapy.

DR. TE LINDE.—I agree with Dr. Miller. There is only one question that I might ask him. How do you differentiate between those to whom you give preoperative radiation and those to whom you do not? I find this distinction difficult, so we routinely use preoperative irradiation. I could entirely agree with him on what he says about vaginal recurrences. I have not seen a vaginal recurrence in any of the cases to which we have given preoperative intracavitary irradiation.

DR. MILLER.—In my desire to be brief I may have cut a few corners. I reported to you on our five-year survival rates. Since we published that report we have individualized our patients to a greater degree and our criteria for whether or not we shall use preoperative irradiation are three in number: If the uterus is not enlarged, if the duration of the symptoms is limited to a short time, and if the histological picture is that of a Grade I or a Grade II carcinoma, we today may go ahead directly with surgery. But we still see mostly advanced cases in the sense that the symptoms have been present for more than six months, so most of our patients with endometrial carcinomas are given preoperative irradiation, customarily x-irradiation.

DR. RALPH W. GAUSE.—May I ask a question about benign tumors? I would like to ask Dr. Te Linde when he would choose hysterectomy over myomectomy.

DR. TE LINDE.—In our Negro ward in Baltimore, it is a very rare thing to do a myomectomy for the reason that in a tremendous percentage there is already sterilization by salpingitis. In private practice, on the other hand, I do a reasonable number of myomectomies. I do not rush in whenever I find myomas present in a woman who wants to have babies. These patients are given a thorough trial to get pregnant, worked up completely from the sterility standpoint, but if there are myomas the size of golf balls, and the patient has remained sterile after a good trial to become pregnant, I think myomectomy is justifiable in the treatment of sterility. On the other hand, if I see a young woman who has recently been married and who has a good-sized fibroid and I believe that the presence of the myoma is likely to interfere with the course of pregnancy I think a myomectomy is indicated at once.

QUESTION: Is hysterectomy ever indicated primarily for sterilization?

DR. ALDRIDGE.—It is assumed that this question refers to a woman in whom the uterus and menstrual functions are normal. In such circumstances hysterectomy is definitely contraindicated for sterilization or to satisfy a woman who is tired of menstruating. Unnecessary removal of the uterus in a young woman may lead to physical and emotional symptoms which are troublesome for both the patient and the surgeon.

DR. FALK.—At the time of a complete abdominal hysterectomy in a woman 35 years of age or older who has children, would you leave ovaries moderately involved by endometriosis if they had caused no symptoms?

DR. ALDRIDGE.—The best treatment for endometriosis is to stop the production of ovarian hormones. We have convincing evidence that ovarian function continues after complete abdominal hysterectomy. Endometriosis involving ovaries may progress after the uterus has been removed and require another operation for relief of symptoms. The only purpose in conservative treatment of ovarian endometriosis is to preserve the menstrual and childbearing functions. At the time of hysterectomy it seems logical to remove ovaries moderately involved by endometriosis even though they have caused no preoperative symptoms.

DR. TE LINDE.—I think there is a situation that falls in between the extremes that Dr. Aldridge talked about and I think that is what Dr. Falk had in mind. In a woman in her mid-thirties for example, who has had all the children she wants or has been sterile, has a completely destroyed ovary on one side and a bit of endometriosis in the other ovary, I would remove the destroyed ovary, resect a part of the other ovary, and do a total hysterectomy. Her chances of being comfortable would be greater than if the uterus were left in and yet she would not be thrown into the menopause.

I can give you our figures. In the cases in which we were "totally conservative," I mean the group in which we saved the uterus as well as one tube and ovary so that childbearing was at least theoretically possible, 12.2 per cent, and in those cases in which we were semiconservative, that is, did a hysterectomy but saved at least some ovarian tissue, 4.4 per cent required further surgery.

QUESTION: It is my impression that Dr. Te Linde leans favorably toward the use of radium in carcinoma of the cervix. I would like to ask him what is his feeling about intracavitary radiation for the treatment of fibromyomas.

DR. TE LINDE.—I think radium has a place in the treatment of fibromas. Here is a typical example: a woman, 45 to 46 years old, with a small bleeding fibroid. She has been previously curetted, and carcinoma of endometrium ruled out. The cervix has been biopsied and carcinoma of the cervix excluded. She continues to bleed. That individual to me is a good candidate for intracavitary radiation.

Sometimes I give such a patient a choice. If she is prejudiced against irradiation I'll do a vaginal hysterectomy. If the woman says, "I don't mind having radium and hate to be tied up for a few weeks, I want to do this the quickest possible way," I have no objection to irradiation. On the whole the results are very good. The same thing applies to functional bleeding. When functional bleeding recurs to the extent that definitive treatment is indicated, intracavitary radiation in people near the menopause is very good.

I do object, however, to doing a hysterectomy, vaginal or abdominal, for functional bleeding at the first offense without a curettage and a study of the endometrium.

QUESTION.—Do you consider postmenopausal bleeding an indication for hysterectomy if uterine curettings are negative for malignancy?

DR. ALDRIDGE.—Uterine curettage is not always a satisfactory or reliable diagnostic procedure for a woman who has postmenopausal bleeding and uterine fibroids. This is especially true if the fibroids are of the submucous variety producing an irregular uterine cavity. The incidence of endometrial carcinoma in such patients is about 50 per cent. It is probably wise to treat such patients with hysterectomy or irradiation.

It is now generally agreed that hysterectomy produces better results than irradiation and that it is the treatment of choice for good-risk patients.

Physical studies of some patients who have postmenopausal bleeding will show obesity, diabetes, vascular hypertension, and degenerative disease which

make them poor surgical risks. For these patients, intracavitary radium may produce excellent results if the fibroids are not too large. If the fibroids are large it may be necessary to accept a calculated surgical risk and to remove the uterus.

DR. LOCKE L. MACKENZIE.—I would like to ask Dr. Te Linde a question. Does he believe that basal-cell hyperactivity is a precancerous lesion?

DR. TE LINDE.—That is the hardest question we have been asked tonight, the hardest one for me even to attempt to answer and we do not know the final answer but this I can say. Basal-cell hyperactivity is frequently found in the neighborhood of true carcinoma in situ. Basal-cell hyperactivity is frequently found around the periphery of true invasive cancer. It is a red flag. When we find it we rebiopsy and we keep that patient under observation for several months but do not make a final diagnosis until the histological findings meet our criteria for carcinoma in situ.

On the other hand, we have had some cases of basal-cell hyperactivity that we have followed for several years and rebiopsied and we have never found it again. So I think we have to consider it a warning, at least temporarily, and possibly a reversible condition.

PRESIDENT MCLANE.—The hour is getting late. Dr. Miller would like to say a few words in closing on some of the larger problems in gynecology.

DR. MILLER.—I am making a plea on behalf of gynecology of the future. As you have listened here tonight you have heard a variety of answers to some of today's gynecological problems. These replies recalled for me a little story I heard this summer in Europe about the alumnus who came back to his medical school after an absence of 25 years. He went in to see one of his professors whom he liked and as he walked into the office the professor came in, threw some blue books on the table and as he did so a piece of paper fluttered to the floor. The alumnus picked up the paper and looked at it. He noticed there were typed examination questions on it and he perused them. He began to recollect that they were exactly the same questions the professor had asked his class. He commented to the professor on this observation, whereupon the professor said, "Yes, the questions are the same but the answers are different." As time goes on our answers change.

I mention this because there are many young gynecologists and obstetricians in this room. The answers of today may have to be changed tomorrow, all of which permits me to raise what I believe to be a pertinent question. What is the future of gynecology? I believe the answer to this question devolves upon each and every one of us who practices this specialty. It is up to every one of us to see that the frontiers of our specialty are broadened.

We have spent a whole evening on the subject of hysterectomy. We might well do so because it is an important aspect of our work. But hysterectomy is only one aspect of gynecology. It seems to me that we as a group have narrow sights, that it is time for us to raise our sights. There are many things that need to be done. We still do not know how to do a really good myomectomy and avoid trouble. In all cases of ectopic pregnancy we take out the tube. Perhaps we could learn how to preserve it. In so-called dysfunctional bleeding we remove the uterus but there may be nothing at all wrong with the uterus. We remove the uterus because we still do not know how to get at the real fault. We should be working to find the factors truly responsible. How much time have we spent on the removal of fibroids ? A great deal, yet is it not about time we spent a little effort trying to figure out why some of these things occur?

Gynecology has a future but its scope and character will depend a great deal upon our own efforts and the lifting of our sights!

VAGINAL INJURY DUE TO COITUS

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LACERATION or rupture of the vagina may occur during sexual intercourse. Although this accident is uncommon, it has been described before and several good reviews concerning this subject are available.[6, 7, 11, 13, 14, 17, 19] It is the purpose of this report to summarize 14 cases of vaginal injury due to coitus treated at Parkland Memorial Hospital since 1947, to tabulate recent cases reported in the medical literature, and to emphasize the importance of this injury as a gynecologic entity.

To avoid needless repetition, the important points of each case report are summarized in Table I. There were no deaths in the series.

Comment

Injury to the vagina during coitus usually occurs at either the introitus or the vaginal vault.[6, 13] Lower vaginal injuries are most often seen in young women as a result of rape or first intercourse. Tears of the vaginal vault are usually found in women who have had intercourse and who have often borne children. In some instances both the lower and upper parts of the vagina are involved, usually as a result of extension of the laceration.

In 1948 Diddle[7] collected 135 cases of rupture of the vaginal vault due to coitus and in Rahm's series[17] 75 per cent of the cases involved the upper vagina. In this group, one tear was limited to the left fornix while 10 others involved the right side or extended across the entire posterior fornix. The peritoneum was exposed in 2 instances and in 5 patients the tear extended from the vault to the lower vagina along the vaginal sulcus. In no instance was there an isolated anterior fornix injury. In 2 cases the tear was limited to the lower vagina. Both of these lacerations were the result of the first intercourse after marriage.

Apparently there is an anatomic explanation for the large number of tears limited to the vaginal vault, especially the right side. Dickinson[6] pointed out that the upper vagina is unsupported except for bundles of connective tissue which lie anterolaterally and make up the base of the broad ligament. The right fornix is larger than the left and because of pocketing of the glans, is probably stretched most during coitus. Once the tear is initiated, extension may occur across the posterior fornix to the opposite side and down the vaginal sulcus.

A number of different factors seem to predispose to this accident. The frequent occurrence of vaginal rupture in pregnant or postpartum patients is

TABLE I. VAGINAL INJURY DUE TO COITUS, PARKLAND MEMORIAL HOSPITAL, 1947-1954

TABLE I. VAGINAL INJURY DUE TO COITUS, PARKLAND MEMORIAL HOSPITAL, 1947-1954

IDENTITY	AGE	GRAVIDITY PARITY	SYMPTOMS	LOCATION OF INJURY	TREATMENT	REMARKS
M. C. PMH-W50083	20	Gravida v Para v	Vaginal bleeding immediately after coitus	4 cm. laceration of rt. posterior fornix	Suture	9 weeks post partum
D. B. PMH-W15152	26	Gravida v Para iv	Profuse vaginal bleeding immediately after coitus; shock	4 cm. laceration of rt. posterior fornix	Suture; transfusion	12 weeks pregnant; 2,000 c.c. blood loss
E. W. PMH-76608	21	Gravida iii Para iii	Vaginal bleeding following coitus	2.5 cm. laceration of rt. posterior fornix	Suture	7 weeks post partum
M. C. PMH-29848	25	Gravida vi Para v Abortion i	Profuse vaginal bleeding after coitus; shock	3 cm. laceration of rt. fornix	Vaginal pack; transfusion	8 weeks post partum
J. W. PMH-95838	17	Gravida ii Para ii	Persistent vaginal bleeding following coitus 9 days before; shock	Entire posterior fornix and left vaginal sulcus	Suture; transfusion	8 weeks post partum
L. B. PMH-61824	71	Gravida xiii Para xiii	Profuse vaginal bleeding following coitus; shock	5 cm. laceration of posterior fornix	Oxidized gauze pack; transfusion	23 years postmenopausal
R. G. PMH-82099	48	Gravida 0 Para 0	Profuse vaginal bleeding after coitus	4 cm. laceration of vaginal apex and rt. vaginal wall	Vaginal pack	Total hysterectomy 22 years before; intoxicated
D. M. PMH-66089	16	Gravida 0 Para 0	Profuse vaginal bleeding following coitus	8 cm. laceration of entire posterior fornix and left vaginal sulcus	Suture	Vigorous coitus
C. S. PMH-101378	18	Gravida 0 Para 0	Vaginal bleeding after first coitus; shock	Laceration at 4, 6, 9, 12 o'clock extending from hymen to upper third of vagina	Suture and vaginal pack; transfusion	Previously virginal
B. J. PMH-86300	11	Gravida 0 Para 0	Vaginal bleeding following rape	6.5 cm. laceration of left posterior fornix and vaginal sulcus	Suture; antibiotics	Menses established for several months
A. B. PMH-104135	13	Gravida 0 Para 0	Vaginal bleeding immediately after coitus	4 cm. laceration of posterior fornix	Suture; antibiotics	Peritoneum exposed; vigorous coitus
B. S. PMH-W27504	19	Gravida 0 Para 0	Vaginal bleeding after first coitus	4 cm. laceration of fourchette, rt. vaginal wall, and suburethral area	Suture	Married 1 week
K. Mc. PMH-W5523	46	Gravida ii Para ii	Profuse vaginal bleeding after coitus	8.5 cm. laceration of entire posterior fornix and rt. vaginal sulcus	Suture; antibiotics	Vigorous coitus while intoxicated
J. M. PMH-W9283	31	Gravida vi Para vi	Profuse vaginal bleeding after coitus	Entire vaginal vault	Suture	3 days after vaginal hysterectomy; intestines exposed through disrupted vaginal vault

TABLE II. VAGINAL INJURY DUE TO COITUS (REPORTED IN THE LITERATURE), 1947-1954

AUTHOR	NO. OF CASES	AGE	LOCATION OF INJURY	REMARKS
Arje and Gilliland[1]	1	22	Right anterior fornix	5 weeks post partum
Burdman[2]	1	17	Posterior fornix	14 weeks post partum
Conde[3]	2	33	Posterior fornix	8 weeks post partum
		25	Posterior fornix	12 weeks post partum
Cope[4]	2	24	Right fornix	Married
		59	Posterior fornix	Postmenopausal
Courtois and Bally[5]	1	24	Posterior fornix	3½ weeks post partum; lactating
Lask[8]	1	57	Posterior fornix	15 years postmenopausal; cul-de-sac ruptured with prolapsed loop of intestine
Lombardi[9]	1	38	Left fornix	Menopause at age 33
Mahon[10]	1	27	Right fornix	8 weeks post partum
Marchetti[11]	1	23	Hymen and both vaginal walls	First intercourse
Mikulicz-Radecki[12]	1	44	Posterior fornix	Married; para iii
Nobile[14]	6	34	Right fornix and sulcus	Unmarried; nulligravida
		23	Right fornix	First intercourse
		30	Right fornix and sulcus	Nulligravida; married 2 months
		40	Posterior vaginal wall	3 years postmenopausal; married; nulligravida
		50	Right fornix	Postmenopausal
		35	Left fornix to middle third vagina	Married 2 days
Oeconomos[15]	3	39	Left fornix	Treated by hysterectomy
		29	Left lateral vaginal wall	First intercourse
		55	Left fornix	Previous subtotal hysterectomy
Pacchiani[16]	1	19	Posterior vaginal wall perforating rectum	First intercourse; standing position
Ravera[18]	1	19	Apex of vagina and perineum	Laceration of a transverse vaginal septum at upper third of vagina and second-degree perineal laceration
Rendelstein[19]	33	?	Vault and hymen	No detailed case reports; discussion of etiology
Sant'Anna[20]	2	?	Anterior fornix	Single, nulligravida
		27	Posterior fornix	Primigravida. Author describes 11 other cases reported in Brazil
Scherer[21]	3	?	All posterior fornix	One at first intercourse and 2 others at 6 and 8 weeks post partum
Serment and Deturmeny[22]	4	20	Posterior fornix	Deaf mute—no history
		34	Posterior fornix	Multiparous
		52	Posterior fornix	Postmenopausal
		64	Posterior fornix	Postmenopausal

TABLE II—CONT'D

AUTHOR	NO. OF CASES	AGE	LOCATION OF INJURY	REMARKS
Speert[23, 24]	4	20	Right fornix	8 weeks post partum
		28	Right fornix	First intercourse
		24	Posterior fornix	Single; nulligravida
		72	Right fornix	Postmenopausal
Stange[25]	2	57	Posterior fornix	Postmenopausal; sexual abstinence for 10 years; vaginismus
		26	Posterior fornix and left sulcus	Husband had Peyronie's disease
Strasheim[26]	1	23	Left fornix	Nulligravida; vigorous intercourse

attributed by most authors to the increased friability of the tissues of the genital tract coincident with gestation. This diagnosis may be missed if speculum examination is not performed routinely on pregnant or postpartum patients who have bleeding episodes. Occasionally attempts at self-induced abortion may cause injuries to the vault but these efforts do not usually produce the characteristic linear posterior fornix lacerations.

Shortness of the vagina due to postmenopausal atrophy or as a result of total hysterectomy must also be considered as a predisposing factor. Intercourse during the early postoperative period following hysterectomy may also easily disrupt the vaginal vault suture line. Rahm[17] believed vaginismus may play a role in the etiology of vaginal tears by shortening and narrowing the vaginal tube. It has also been suggested that during excessively vigorous intercourse, increased intra-abdominal pressure on the part of the female partner may tend to make the cul-de-sac tense and lessen the elasticity of the posterior fornix during deep penetration.

Genital disproportion is doubtless an important cause of vaginal laceration, especially in pubertal girls, nulligravidas, and young women at first intercourse. There were 4 cases of rupture of the vagina following coitus treated at Parkland Memorial Hospital during the period covered by this report which are not mentioned here, since they occurred in prepubertal girls following rape and were obviously the result of gross genital disproportion. In all the cases reported, normal menses had been established.

Positions during intercourse in which unusually deep penetration is experienced, i.e., dorsal decubitus with hyperflexion of the thighs and sitting positions, may also play a role in the etiology of this injury. No positions other than the dorsal decubitus were admitted by any of the patients reported here, however. Other predisposing factors which have been noted by various authors are uterine retroversion, undue haste on the part of the male, brutality, drunkenness, vaginal scars, and genital malformations.

Treatment of this injury is simple and consists of either suture of the laceration or insertion of a vaginal pack. The former method is certainly preferable since it allows rapid healing, controls bleeding quickly, and decreases the chance of infection. Blood replacement and antibiotics are used as needed.

There were no deaths in any of the patients reported but five showed evidence of hemorrhagic shock and required blood replacement.

Since 1947, at least 72 cases of vaginal injury due to coitus have been reported in the world literature and these are summarized in Table II.

Conclusions

1. Serious vaginal injuries due to coitus may occur.

2. Factors which predispose to this accident are: pregnancy, vigorous intercourse, coital positions in which unusually deep penetration is experienced, vaginismus, genital disproportion, postmenopausal atrophy, recent or remote gynecologic operations, uterine retroversion, brutality, drunkenness, vaginal scars, undue haste on the part of the male, and genital malformations.

3. The vaginal vault, especially the posterior fornix, is most often the site of injury. Other portions of the vagina are less often involved.

4. Fourteen cases of vaginal injury due to coitus which were treated during the years 1947-1954 at Parkland Memorial Hospital, Dallas, are reported.

5. Seventy-two similar cases reported in the world literature during the same period are summarized.

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CONCEPTION CONTROL

A Clinical Evaluation of the Preceptin-Gel Method

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THIS study was prompted by the wish to evaluate a method of conception control which seems to be simpler and to have greater patient acceptability than previous methods. The need for planning the size of family groups and the methods used to attain the limitation of family size have been known for centuries. It has been only in recent decades, however, that society has recognized the right of individuals to attempt this control of the number of children which they consider desirable or suitable to their position in the community. An early study[8] showed that 90 per cent of the couples under consideration tried to control pregnancy in some manner. There is wide difference of opinion regarding the most desirable manner of such control but the fact must be apparent to all of us that conception control is an accepted part of our social structure today.

Many methods have been suggested through the years, ranging from the act of withdrawal and rhythm methods, to the diaphragm and jelly method. Tietze[7] made an extensive statistical study of the effectiveness of the various methods and his results are shown in Table I. He further pointed out that the practical effectiveness of any method depends upon many factors which are difficult to evaluate: these variables include the educational, social, and economic levels of the couples involved, and the motivation for receiving the contraceptive information; that is, was it more or less forced upon the patient or was it sought voluntarily?

TABLE I. PREGNANCY RATES PER 100 YEARS OF EXPOSURE FOR VARIOUS METHODS*

METHOD	PREGNANCY RATE
Withdrawal	12-38
Rhythm	14
Postcoital douche	36
Foam powder and sponge	27-33
Suppositories	17-27
Diaphragm and jelly	6-29
Jelly alone	9-38
Condom	6-19
Cervical cap	8

*From Tietze.[7]

Many studies of contraceptive methods and many physicians today try to measure the effectiveness of a method in terms of successful and unsuccessful users. Such evaluations, however, have failed to note a vitally important factor, the duration of exposure to the risk of pregnancy. A group of couples who

have successfully relied upon some specific contraceptive method for a long period of time have obviously been exposed to pregnancy much more than another group using the same method for only a short period. The first group, therefore, is of considerably greater value in determining the effectiveness of any method under consideration. To make allowance for this time factor Raymond Pearl[5] devised a formula for computing the pregnancy rate per 100 years of exposure. To determine this rate for a group of cases one first ascertains for each couple the duration in months of exposure to the risk of pregnancy. These months of exposure are then added and the pregnancies of all couples under observation are noted, and the pregnancy rate per 100 years of exposure is computed by the formula:

$$\text{Rate} = \frac{\text{Number of pregnancies}}{\text{Total months of exposure}} \times 1200$$

Many authors have distinguished between what they call "method failures" and "patient failures" and have obtained comparatively low pregnancy rates per hundred years of exposure by eliminating the so-called patient failures. It seems illogical to exclude a pregnancy because of the patient's irregularity or complete omission of contraception, when the nonpregnant users are not also excluded for the same reasons. In discussing this aspect, Gamble[2] felt that all investigators must exclude the irregular or careless users who do not become pregnant, if they insist on excluding those in this group who do happen to become pregnant.

In this regard, Tietze[7] concluded, "It is therefore recommended that, in computing pregnancy rates, all exposures and all conceptions be included up to the time when the couple decides to abandon contraception entirely or to change the method." This recommendation seems a very wise one and the figures of this present study have therefore combined all failures under one classification.

In any study of the effectiveness of a contraceptive method, one must attempt to establish some method of control. It is obvious that it is almost impossible, however, to determine the uncontrolled fertility of any group of individuals which then might be compared with the fertility of any group using a contraceptive method. Tietze[7] reports the use of the census of Canada for 1941, where women in the rural areas of Catholic Quebec were studied and used as an adequate group demonstrating uncontrolled fertility. These women were at least 45 years old at the time of the census enumeration, had been married an average of 27 years and, allowing for 10 per cent pregnancy wastage, had averaged almost twelve pregnancies in the 27 years of their marriage. This corresponds to a pregnancy rate of 65 per 100 years of exposure, and should be remembered when other rates are quoted for various methods of conception control.

The ideal contraceptive has not as yet been discovered. None of those now available have reached the maximum simplicity and effectiveness. There is a constant striving by many research investigators toward the ultimate goal of the perfect contraceptive method, one that will allow proper spacing of

children with confidence, and yet will allow conception readily when its use is discarded. It must also be simple, cheap, harmless, and acceptable to peoples of diverse cultural backgrounds. This ultimate method may come from the use of enzymes, hormones, or perhaps plant extractives.

An additional forward step toward this goal was made in 1949 with the introduction of a vaginal jelly whose principal active ingredients are paradiisobutylphenoxypolyethoxyethanol and ricinoleic acid. The manufacturers of this preparation offered it as a method which could be used alone without the addition of other contraceptive measures. Well-recognized authorities in the field of conception control have published a number of studies relative to the effectiveness of this new jelly known as Preceptin.*

All of these publications have been unanimous in their conclusions that, from the patient's point of view, the gel-alone method is certainly a most acceptable and simple one. The question remaining, therefore, is whether or not this method is as effective in preventing pregnancy as the more time-honored methods of diaphragm and jelly, or condom.

Material

This is a study of 326 patients from private practice who visited the office for contraceptive advice, either post partum or otherwise. Specific instructions were given in the use of Preceptin gel alone, only to those patients not requesting some other method. No attempt was made to force the use of Preceptin on a patient satisfied and successful with another contraceptive method.

This patient group represents a random sample of an urban private practice, chiefly one of middle income economic status. All were white, of average or above-average intelligence and schooling.

The patients all received a complete pelvic examination prior to being instructed in the use of the contraceptive agent. Then all patients were similarly instructed in the use of the gel according to the method described by Stromme and Rothnem,[6] as follows:

1. Introduce a full applicator of Preceptin deep into the vagina. Press in the plunger and then remove the applicator without drawing back on the plunger. The gel may be introduced up to one hour before intercourse. If desired, intercourse may immediately follow the introduction of the gel.
2. If intercourse is repeated after a lapse of more than one hour, an additional applicatorful is necessary.
3. Douching is optional but should not be done until at least six to eight hours after the insertion of the jelly.
4. Use the jelly before each time of intercourse; even one omission may cause failure.

Follow-up was obtained through questionnaires which serve as the basis for this report.

Of the 326 patients who were given this contraceptive advice and were sent questionnaires, 211 responded.

The questionnaire itself was anonymous so as to encourage a wider expression of opinion, although many were returned signed and with pertinent and elaborate comments, a fact which seems to point to the interest and attention of this particular patient group to the study being conducted.

*Ortho Pharmaceutical Corp.

It is important in this connection, however, to note that the anonymity of the questionnaire provided many difficulties in evaluating the results of the study. None of these patients knew that they would be made members of the study group at the time they were instructed in the use of Preceptin, and none of them were told they would be questioned at a later date. When the questionnaires were answered by them, therefore, many depended exclusively on their memory and their personal opinionated convictions.

It was also impossible to discuss any of their replies with the patients and this fact makes it particularly difficult to evaluate the factor of motivation in any given patient's use of a contraceptive. There was sufficient response to the questionnaire, and enough accuracy to the data received, however, to validate the survey which is herewith presented.

The questions asked the patients were as follows:

1. Your age _____
2. How many children have you had? _____
3. Are you still using Preceptin? Yes____ No____
   a. As your only method of birth control? Yes____ No____
   b. In combination with other materials? Yes____ No____
   What materials? _____
4. For how many months have you used Preceptin satisfactorily? _____
5. Has Preceptin been more pleasant to use than other methods with which you are familiar? Yes____ No____
6. Have you become pregnant since being instructed in the use of Preceptin? Yes____ No____
   a. By choice? Yes____ No____
   b. By failure of Preceptin? Yes____ No____
   Please give details _____
7. If your pregnancy was by choice, how long was the interval between the time you discontinued Preceptin and the time you became pregnant? _____ (months)
8. If you have discontinued the use of Preceptin, will you please state your reasons below:
   _____

Of the 211 patients who replied, 14 patients failed to use the method, 19 patients used the method only in conjunction with some other method of contraception, and 11 patients used the method less than 3 months. The patients who did not use the method and those who used it in conjunction with other methods of contraception can automatically be eliminated from any further consideration in this discussion. Of the 11 patients who used the method less than 3 months, 6 discontinued it because of "no confidence," 1 because of its being "too messy," and 1 because it caused vaginal irritation. The remaining 3 reported that they discontinued the method because it failed to work and they became pregnant within less than one month after instruction. In most similar studies of this type, patients using a contraceptive method less than 3 months are excluded from further discussion or calculation of effectiveness, thus eliminating patients pregnant at the time they were instructed, or patients only mildly interested in the use of the method. Accordingly we shall exclude the 11 patients in this category from further consideration.

The remaining 167 patients, therefore, used Preceptin as their only contraceptive method for periods varying from three to fifty months. One hundred and fifty-nine of this group, 95.2 per cent, were of known fertility, having had from one to five full-term pregnancies. The age distribution of these 167 patients ranged from 19 to 45 and the breakdown by age groups is shown in Table II.

TABLE II. AGE DISTRIBUTION OF ACTIVE USERS

AGE (YEARS)	NUMBER	PER CENT
15-19	1	0.6
20-24	20	12.0
25-29	55	33.0
30-34	50	29.8
35-39	27	16.2
40-44	13	7.8
45-49	1	0.6
Total	167	100.0

Twenty-one of the 167 patients discontinued the use of Preceptin after using it for three months or more. Twenty of these women, however, stopped the method after using it less than six months, and the method has not been discontinued by any patient who used it for longer than eight months. The reasons for discontinuing the method are shown in Table III.

TABLE III. REASONS FOR DISCONTINUING PRECEPTIN METHOD

REASON	NUMBER OF PATIENTS
"Too messy"	10
"No confidence"	6
"Religion"	3
Vaginitis	1
"Inconvenient"	1
Total	21

This study bears out the observation from several previous studies of contraceptives, namely, that the gel-alone method has a widespread patient acceptance. One hundred and thirty-eight (82.6 per cent) stated that this method was more pleasant to use than other methods with which they were familiar. The comments of the patients regarding acceptability are recorded in Table IV.

TABLE IV. PATIENT ACCEPTANCE

COMPARISON WITH OTHER METHODS	NUMBER OF PATIENTS	PER CENT
"More pleasant"	138	82.6
"Less pleasant"	15	9.0
"Not familiar with others"	3	1.8
No comment	11	6.6
Total	167	100.0

In this total of 167 active users there was another group of 46 patients who discontinued the use of Preceptin and became pregnant by choice. The interval between the discontinuance of Preceptin and the onset of their pregnancy varied between "immediate" and 27 months. These intervals are shown in Table V.

Thirty-two (69.5 per cent) of these patients became pregnant in three months or less after discontinuing the use of the method. It is also of interest to note that only 8 of these patients tried more than six months to become pregnant. The results in the entire group of 167 active users are shown in Table VI.

Among this group of active users there were 26 method failures and 2 patient failures. This ratio of method failures to patient failures is far out

of proportion to that reported in other studies, but, as we have previously pointed out, the distinction between the two groups is a false one and actually should never be made.

If we then refer back to the Pearl formula for calculating the pregnancy rate, we find that our rate is calculated as follows:

$$\text{Pregnancy rate} = \frac{\text{Number of pregnancies}}{\text{Total months of exposure}} \times 1200$$

$$\text{Pregnancy rate} = \frac{28}{3280} \times 1200$$

$$\text{Pregnancy rate} = 9.5 \text{ per } 100 \text{ years of exposure}$$

Comparing these figures with those given in the most recently published study on the Preceptin method of contraception by Finkelstein, Guttmacher, and Goldberg,[1] we find that their total pregnancy rate was 11.0 per 100 years of exposure. Their study was conducted in a clinic population sample. Earlier studies on this method of contraception include that of Hunter, Darner, and Gillam[4] who reported 29 total failures among 203 patients who responded to questionnaires. This study is comparable to the present one in that it represents a private patient group. Another earlier study which represents a combined clinic-private patient group was reported by Stromme and Rothnem.[6] Their pregnancy rate based on users of two months or more is calculated as 4.1 per 100 years of exposure.

TABLE V. PLANNED PREGNANCIES

TIME INTERVAL (MONTHS)	NUMBER OF PATIENTS	MONTHS METHOD WAS USED BY EACH PATIENT PRIOR TO PREGNANCY
Immediate	4	10-40-42-48
One-half	2	7-12
One	15	3-9-11-12-12-13-13-16 16-17-18-20-20-28-36
Two	8	18-20-27-28-30-33-36-36
Three	3	14-24-24
Four	4	4-17-18-18
Five	1	19
Six	1	12
Seven	3	17-19-36
Eight	1	24
Twelve	1	12
Eighteen	1	30
Twenty-seven	1	9
"Don't know"	1	36
Total	46	964

TABLE VI. RESULTS IN 167 PATIENTS WHO USED PRECEPTIN METHOD FROM 3 TO 50 MONTHS

MONTHS USED	TOTAL PATIENTS	METHOD STOPPED	ACTIVE USERS			TOTAL MONTHS USED
			NO PREGNANCIES	PLANNED PREGNANCIES	FAILURES	
3-6	33	20	2	2	9	141
7-12	32	1	12	10	9	336
13-18	25		8	12	5	392
19-24	23		13	8	2	512
25-30	20		13	5	2	559
31-36	18		11	6	1	637
37-42	9		7	2		361
43-48	5		4	1		240
49-50	2		2			100
Total	167	21	72	46	28	3,280

Comment

Clinical evaluation of any contraceptive agent is most difficult. Certainly there seems to be no question about the predominant acceptability of the gel-alone method. Remembering that Tietze[7] said the pregnancy rate per 100 years of exposure is the best available measure of the use-effectiveness of contraceptive methods, let us consider how the results of our study compare with pregnancy rates as determined by others.

As has been mentioned previously, our total pregnancy rate of 9.5 is considerably higher than that of Stromme and Rothnem[6] who reported a rate of 4.1 in a combined clinic-private patient group. The total pregnancy rate was 11.0 in the Finkelstein[1] study and 9.5 in our group, but it must be remembered that the two studies represent different population samples with data being collected differently. Since our study represents a more favorable population sample than either the Stromme or Finklestein group, it might be expected that our pregnancy rate would be significantly lower, but this has not been borne out by this study. This fact may possibly be explained by our questionnaire method of collecting information.

However, in a comparison of our pregnancy rate of 9.5 with that reported by other investigators where other methods of contraception were used, as shown in Table I, it is seen that the Preceptin method appears in a very favorable light. In order to compare more accurately the Preceptin method with various other methods of contraception there is a need for additional clinical studies where similar population groups using different contraceptive methods are compared, and where the data have been collected in a uniform manner.

Tietze says that the chance of conception within one month after discontinuance of any contraceptive measure is between one in four (0.25) and perhaps three in ten (0.30) per month. Our pregnancy rate of 9.5 per 100 years of exposure, when reduced to pregnancies per month, equals $\frac{9.5}{1200}$, or 0.008 per month of exposure. If the chance of pregnancy per month, however, after stopping a contraceptive is taken as 0.25, then our rate represents only 3.2 per cent of this figure. It follows, therefore, that this percentage taken from 100 per cent, or 96.8 per cent, represents the amount by which Preceptin has reduced the likelihood of pregnancy in our group of patients.

New methods of contraception are frequently looked upon with suspicion by the physician, with the result that a lack of confidence in such methods is created in the patients using them. It appears from this study that Preceptin is as effective in preventing conception as other methods now in common usage. Since no single method of conception control is applicable to all patients it seems that the Preceptin method should become a part of the armamentarium of physicians who are interested in this problem of family planning.

Summary

1. A questionnaire-type study has been carried out to evaluate the effectiveness of Preceptin in a private-practice population group.

2. There were 9.5 pregnancies per 100 years of exposure in 167 women who used this method exclusively.

3. This rate, while not as favorable as a few previously reported on the use of Preceptin, compares quite favorably with some others on Preceptin as well as many reports on the use of other methods such as diaphragm-jelly, condom, and cervical cap.

4. The Preceptin-gel method of contraception reduced the likelihood of conception by 96.8 per cent.

5. Further clinical studies are needed to compare similar population groups.

We wish to express our deep appreciation to Dr. Katherine Kuder for her help and critical evaluation of the material used in this study. We also wish to thank Mr. Luis J. Nanni, Professor of Statistics, Rutgers University, for his analysis of the statistics presented.

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ENDOMETRIOSIS. DEMONSTRATION FOR THE SAMPSON THEORY BY A HUMAN ANOMALY

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THE Sampson theory for the etiology of endometriosis is now quite generally accepted by gynecologists. It is thought to offer the most likely explanation for the development of at least a large part of these interesting lesions.

This acceptance has resulted from thirty years of clinical observation and painstaking experimental work recorded by numerous investigators.

The obvious essentials to make the Sampson theory tenable have been the following:

1. Proof that viable endometrial cells are found in menstrual blood.
2. Proof that endometrial cells will grow when transplanted as autogenous grafts to host tissues where endometriosis usually develops.
3. Proof that retrograde menstruation through the tubes occurs.

The production of endometriosis experimentally in lower animals is now recorded in medical literature.[1] To complete the chain of evidence, only the experimental production of endometriosis in human beings is lacking. The opportunity to record such evidence constitutes the reason for this paper.

One of our most respected gynecologists[2] wrote in 1926, "Dr. Sampson's theory would be greatly strengthened if he could demonstrate two things: first, the capacity of the degenerated epithelium given off at menstruation to grow in tissue culture; second, the capacity of such endometrium to grow on the peritoneum or the ovary of the human being or perhaps even of one of the lower animals. Both of these proofs are lacking and I am inclined to believe it will be difficult to prove either point experimentally."

Let us then briefly review these requirements in order.

Are viable endometrial cells found in menstrual blood? Early ill-conceived and inconclusive experimental work seemed to prove the negative. Heim[3] opened the uterus of monkeys on the first day of menstruation and scattered the uterine contents over the abdomen and pelvis. He then opened the abdomen fifty-six days later and found no endometrial tissue. He then scattered human menstrual discharge over the abdomen and pelvis of monkeys and forty-six days later found no endometrial tissue. In both experiments there was inadequate time lapse and in the second experiment he was depending upon an heterogenous transplant to prove his point.

More recently, Scott, Te Linde, and Wharton,[1] experimenting with rhesus monkeys, ingeniously established the positive viability of endometrium cast off in menstrual blood. Ten monkeys were surgically altered, without cutting

across endometrial tissue, to permit intra-abdominal menstruation. Five of these ten animals developed typical endometriosis. Since care was taken that no endometrium was transplanted surgically, and since no endometrial tissue was visible at the first opening of the abdomen, this appears to establish the viability of the endometrial cells cast off in menstrual blood.

Second, can it be proved that endometrial cells will grow when transplanted to host tissues where endometriosis is commonly found? The work of Te Linde and his co-workers[1] can again be cited as proof. In earlier work Te Linde and Scott,[4] again working with rhesus monkeys, successfully transplanted bits of endometrium surgically to various points of the abdomen and pelvis, and later found "takes" in the areas transplanted. Jacobson,[5] in similar experiments, and using rhesus monkeys, had previously successfully transplanted endometrium to the abdomen and pelvis. Heim,[3] Coffier,[6] Traut,[7] and Hirsch and Jones[8] had already demonstrated the successful growth of endometrium cultured on various laboratory media.

Third, is retrograde menstruation through the tubes possible? This occurrence has been observed and reported so frequently in human operations done during menstruation that only a skeptic could still harbor doubts.

It appears, then, that menstruation through the tubes does occur, that viable endometrium is found in menstrual blood, and that endometriosis can be developed experimentally in lower animals.

Finally, can endometriosis be produced in human beings? Obviously no surgeon would be justified in performing a transplant experiment on any of his patients, and no such report appears in the medical literature. However, nature seems perversely to have contributed such an experiment and it became my good fortune to have observed this patient.

Case Report

B. R., an unmarried girl 18 years of age, was seen July 17, 1953. She had never menstruated. She complained that for four years she had had severe lower abdominal cramps lasting for three days. These cramps had recurred cyclically about every twenty-eight days. The cramps were accompanied by nausea, and vomiting had frequently occurred during these three-day attacks. She had observed her own temperature and had noted an elevation to 100°–102° F. during the first day of the cramps. There was nothing noteworthy in the past history except that an appendectomy had been done in 1950 for "chronic appendicitis."

Examination.—The patient was found to be a normally well-developed girl of 18 years. The breasts were well developed. The hair distribution was normal. The vaginal examination showed the external genitals to be well formed and normally developed. The introitus was virginal. The urethra was normal. The vagina was of normal width but ended in a blind pouch 5 cm. in depth. There was no visible cervix, the mucous membrane at the normal site for the cervix being smooth and, in appearance, exactly like the rest of the vaginal surface. Bimanual examination disclosed the corpus uteri to be of average size, regular in outline, in well-marked anteposition and freely movable. The lower segment of the uterus narrowed to form a structure the width and length of a normal cervix. This crevix lay approximately 1½ to 2 cm. above the vaginal vault and with no apparent connection with it. Neither tube nor ovary was palpated. There was little pelvic tenderness.

Impression.—A congenital anomaly was obvious which appeared to be associated in a causal relationship with her cyclical cramps. An exploratory laparotomy was advised to identify the extent of the pelvic anomalies and, if possible, to connect the cervix to the vaginal vault.

Fig. 1.

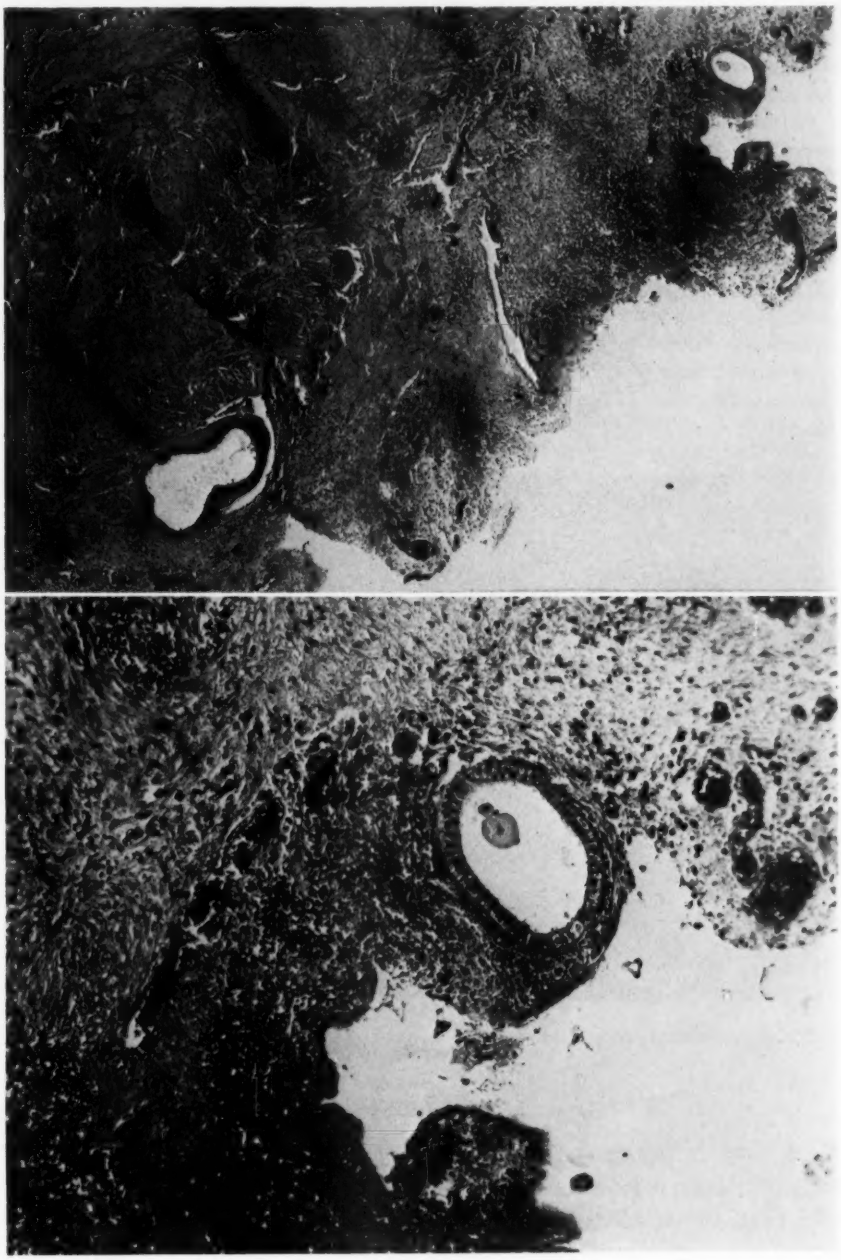

Fig. 2.

Fig. 1.—Low-power photomicrograph of uterus showing serosal and subserosal endometriosis. (×80.)

Fig. 2.—High power of area shown in Fig. 1. (×175.)

Surgical Findings.—On Sept. 1, 1953, the abdomen was opened and the findings were as follows: There was considerable blood and fibrin over all pelvic structures. There was widely distributed pelvic endometriosis. The left ovary presented a moderately large typical chocolate cyst. Endometrial implantations were seen on the surface of the right ovary, over the bladder, sigmoid, and in the cul-de-sac.

Still in the hope of connecting the cervix with the vagina, the cervix was explored. The area intervening between the cervix and vagina appeared to be made up of loose connective tissue. No blood or fibrin was seen in this region. For more minute inspection, the cervix was seized with a towel clamp and rotated upward. No external cervical os was visible, nor was it possible to identify one with a fine probe. Still in the attempt to preserve the uterus and connect the cervix normally, a hysterotomy was done, and identification of a cervical canal from within was attempted. During this procedure the probe entered a small cystic sac in the upper cervix which was filled with dark inspissated blood. Further effort to sound a continuing cervical canal was futile.

Therefore, because of the presence of extensive general endometriosis and the absence of a cervical canal, a total hysterectomy together with a left salpingo-oophorectomy was done. Adhesions were released and the abdomen closed.

Laboratory Findings.—The pathological laboratory confirmed endometriosis of the left ovary, the serosal surface of the uterus, and the subserosal muscularis.

Progress.—The patient made an uneventful recovery and has been entirely relieved of symptoms.

Fig. 3.—Photomicrograph of ovary showing several foci of endometriosis with old and recent hemorrhage. (×80.)

Comment

Here then is presented for the first time in a human being the "experimental" production of general pelvic endometriosis by menstruation through the Fallopian tubes. This experiment was performed by nature in presenting an anomalous absence of a cervical canal, and is closely analogous to the experimental endometriosis in monkeys as recorded by Te Linde and his coworkers.[1] There can be little doubt that this patient's severe, cyclical, twenty-eight-day pain was due to the spill of menstrual blood into the abdominal and

pelvic cavity. The pelvis was filled with blood typical of menstruation at the time of operation. The cervix was sealed and no blood was found in the vicinity of the cervix. Therefore, no exit from the endometrial cavity remained possible except through the Fallopian tubes. For any who might seek to explain the presence of pelvic blood by rupture of an endometrial cyst of the ovary, the cyclical spill, as demonstrated by the patient's regular monthly cramps, would have to presume an unbelievable four-year coincidence.

Summary

1. The requirements to prove the validity of the Sampson theory in the etiology of external endometriosis are enumerated.

2. Experimental work which satisfies these requirements is cited.

3. A case is presented, which by an anomaly seems to offer for the first time in a human female further evidence for the Sampson theory, closely paralleling experimental work with monkeys.

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THE INFLUENCE OF DIETARY SODIUM INTAKE ON WATER, ELECTROLYTE, AND NITROGEN BALANCE IN PREGNANCY TOXEMIA, A METABOLIC STUDY*†

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PROBABLY no process related to obstetric physiology has received greater emphasis than the subject of water and electrolyte metabolism during normal and abnormal pregnancy. While earlier metabolic studies were concerned primarily with water and nitrogen balance in normal pregnancy with the perfection of very reliable methods, practically all such studies excluded considerations of complete electrolyte metabolism. Among patients with toxemias of pregnancy, where balance studies were performed, alterations in water metabolism received special attention, but only isolated reports of nitrogen balance in toxemic patients are recorded. Some relationship between sodium and water metabolism, even though not proportionate, is known to exist in normal pregnancy and in the toxemias of pregnancy.

The advent of flame spectrophotometric methods now makes possible the determination of more extensive, more complete, and more accurate studies of sodium and potassium values as well as of their respective balances. Whereas complete studies of electrolyte, water, and nitrogen balance were commonly lacking in the same patient, the measurement of some of the more common electrolyte balances, coupled with improved methods of determination of water and nitrogen metabolism, permits exploration of possible interrelationships among these various factors.

Any study of the partition of water between the extracellular and intracellular phases must consider the component electrolytes of each space. Changes in either the solute or the solvent render pathologic the physiologic mechanisms of the body. Even though the extracellular fluid is said to comprise 70 per cent of total body weight, no absolutely accurate method of obtaining this value has yet been reported. The determination of inulin space, while providing an acceptable and practical index of the measurement of the extracellular fluid compartment, still does not lend itself to everyday application but is a satisfactory research tool. As yet, the measurement of total body water, even with isotopes, must be considered as a rough approximation. Thus, until more accurate means of measuring total body water are obtained, most values for intracellular fluids still must be considered as approximations.

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That blood volume increases and some water retention occurs in normal pregnancy has been well established. It is also a well-known fact that water and electrolyte retention is a common feature in the toxemias of pregnancy.[14] In general, the conclusions drawn, although apparently obvious, seem to have been reached on clinical grounds alone. Long-term evaluations of patients throughout normal pregnancy are scarce, however. Even when attempts to prove the contention that significant water retention occurs during various periods of pregnancy are made by quantitative measurements of body water, the methods of performing these measurenents often are not entirely satisfactory. The methods employed, in general, are impractical for clinical usage and, even when used as research adjuncts, are somewhat tedious, intricate, and time consuming. Unless the same methods are used throughout a given study, under all conditions in the same study and subject, the results are open to question. Particularly may such results be questioned when one is concerned with the measurement of intracellular fluid by the use of formulas for the calculation of extracellular fluid volume. Even then the same conditions must obtain in the same patient; certainly the edematous state should not be compared to the "dry" state.

Since the capillary walls are permeable to the water of the blood plasma, they are also permeable to all the constituents of blood plasma except the plasma proteins. Therefore, wherever plasma water permeates, so too do the electrolytes of this solution. The only difference then between intravascular fluid and extravascular fluid is the presence in the former and the absence in the latter of plasma proteins. Because of the intravascular location of the circulating and recirculating plasma proteins, the plasma circulation and thus the osmotic pressure within the circulatory boundaries is governed by the plasma proteins.

Chesley[1] summarized balance experiments by various authors and noted that consistent sodium retention occurred during pregnancy. This retention varied from 1.6 Gm. (69.6 meq.) to 8.8 Gm. (382.6 meq.) a week. He found that a representative figure was about 3 Gm. (130.4 meq.) per week; this would mean a retention of water in amounts of slightly less than 1 L. per week, if all this sodium were osmotically active. These balance studies reviewed by Chesley were performed when gravimetric methods for measuring sodium were in vogue, with their attendant multiple opportunities for error; potassium was not included in the analyses. With improved techniques and newer precision instruments available for the determination of all the electrolyte constituents of body fluids, particularly for determining potassium and sodium, we felt that more exhaustive evaluation of complete electrolyte, water, and nitrogen metabolism might extend our knowledge of the interrelationships. In view of the analyses by Bergstrom[2] and by Francis Moore,[3] showing that bone may act as a reservoir for sodium, it is now possible for these considerations to be included in any analysis of water and electrolyte balance to determine whether positive or negative balances actually do occur.

Thompson and Pommerenke[4] showed that fluctuations in sodium and chloride balances were parallel. In our evaluation it was not possible for us to show this correlation and may well again reflect differences in method and possible errors in the determination of sodium.

Freyberg, Reekie, and Folsome[5] showed that the administration of sodium for a few days during pregnancy was accompanied by increased body weight, with a reduction in body weight upon withdrawal of sodium chloride. They also showed very clearly that the variations in body weight were due to retention and to excretion of water. They studied one subject very carefully

during the last three months of normal pregnancy and noted a retention of 600 Gm. of sodium (26,000 meq.); this patient had the lowest of the sodium balances reviewed by Chesley.

Chesley[1] noted that the total gain of extracellular water during pregnancy averaged 6.3 L. He felt that 1.5 to 2 L. were probably in the products of conception, 0.7 L. in the new tissue of the uterus and breasts, and 1.3 L. in the blood plasma. This would leave about 2.5 L. (5.5 pounds) as the share of the extragenital interstitial fluid. With a decrease in the concentration of the plasma proteins, however, the drop in the colloidal osmotic pressure of plasma may be as much as 20 per cent. With this decrease in the concentration of the plasma proteins a great increase in the volume of the interstitial space should occur as a result of its receiving more than its share of the excess water. Since it has been repeatedly shown that the plasma protein is even further decreased in the edematous pregnant patient, an increase of the protein content of the interstitial fluid would further lower the effective colloidal pressure of the plasma. Even though the water content of both the plasma and the interstitial fluid is increased during pregnancy, no demonstration has satisfactorily explained the distribution of the fluid between these two compartments. It may well be that Bergstrom's conclusions regarding osseous tissue acting as a reservoir for sodium will explain the increase in weight associated with an increase in sodium retention. Although such storage in bone contains osmotically inactive sodium, it is quite possible that bone can release sodium for osmotic activity as depletion states occur, whether the depletion be due to excretion or dilution. On the other hand, nitrogen, if it is built into protoplasm, could also account for such increases in weight. In an attempt to clarify possible interrelationships between electrolyte and nitrogen balance and in order to explain some of the increases in weight said to be due to water retention during pregnancy, a patient with mild pre-eclampsia was selected for study.

Case History

Mrs. J. B., a 37-year-old Indian, gravida i, para 0, had an expected date of confinement of Dec. 23, 1953. She was admitted to our In-patient Service on Oct. 19, 1953, because of a weight gain of 12.2 kilograms in a seven-month period, a blood pressure of 144/106, 1 plus edema, and traces of proteinuria. She was placed on a 1,200 calorie, neutral-ash, salt-free diet and on a fluid intake of 4,000 c.c. daily. She failed to lose weight on this regime but instead gained 3.4 kilograms in six days. Her blood pressure dropped, however, to 114/70 but, with the gain in weight, it increased to 134/100. She was then placed on mild sedation and on our full toxemia treatment regime. She developed hyponatremia with serum sodium levels of 128 meq. per liter and associated symptomatology of the low salt syndrome which required sodium replacement on Nov. 6, 1953. The serum sodium levels consistently approximated 130 meq. per liter and by Dec. 1, 1953, her cumulative sodium balance was negative 46 meq., based upon urine sodium excretion compared to measured sodium intake. This figure indicated a daily urinary excretion approximately equal to the amount ingested. On Dec. 2, 1953, the serum sodium level had decreased to 118 meq. per liter, again requiring replacement. Because of this marked lability of sodium balance, she was considered a satisfactory candidate for complete balance studies. She was then transferred to the metabolic ward for study of the effect of a low-sodium diet as well as augmentation of sodium chloride intake on water, electrolyte, and nitrogen balance in pre-eclampsia and specifically for study of mechanisms which might be responsible for the inability to compensate for a low-sodium intake.

Plan of Study

The diet was planned to be compatible with the particular likes and dislikes of the patient and to conform to her caloric needs. Since the patient was overweight, the diet

was designed to contain 1,200 calories and to be high in protein but low in salt. Two separate diets were prepared, as similar as possible but permitting some variety; they were to be eaten on alternate days. At the beginning of the study, food was purchased in large enough quantities for the entire 14 to 16 day anticipated period of study, and the entire amount of any one food was purchased from one lot so as to maintain uniformity. Surplus amounts of meat were preserved in the freezer. The composition of diets is noted in Table I. The values for calories, carbohydrate, protein, and fat were calculated from standard tables by the dietitian. Values for the other components were obtained by analysis of a complete diet, using the same methods and reagents as for urine and stool samples.

TABLE I. COMPOSITION OF DIET

	DIET A	DIET B	MEAN
Calories	1,202.7	1,207.7	1,205.2
Carbohydrate (Gm.)	108.8	154.7	131.7
Protein (Gm.)	90.4	86.7	88.6
Fat (Gm.)	45.1	26.7	35.7
Nitrogen (Gm.)	12.1	10.14	11.14
Calcium (meq.)	89.57	83.72	86.65
Phosphorus (meq.)	87.77	86.47	87.12
Sodium (meq.)	34.38	35.21	34.8
Potassium (meq.)	80.87	74.39	77.63
Chloride (meq.)	39.1	41.0	40.0
Water (Gm.)	1,599.7	1,551.6	1,576.7

The patient had been receiving a low-sodium diet, as designed for patients with toxemia of pregnancy, and calculated to contain approximately 800 mg. of sodium daily. The patient had been on this diet for the six weeks immediately prior to the present study; therefore, no period of adjustment to the metabolic diet was considered necessary. Carmine was used to demarcate the stools corresponding to each study period. It was administered in a gelatin capsule with the bedtime snack at 9:00 P.M. on the evening before the beginning of each new study period. Before breakfast each day, the patient was weighed and blood samples drawn. Blood was analyzed daily for carbon dioxide content, sodium, potassium, chloride, calcium, and phosphorus; in addition, on the first day of each period blood was drawn and analyzed for hematocrit, blood urea nitrogen, and plasma proteins. Blood for determination of carbon dioxide content was collected under oil.

In order to determine insensible water loss and water balance, the weight of the patient was accurately determined daily by the same person on a scale especially constructed for this purpose; and the weights of all ingesta and excreta were accurately measured with special precautions taken to avoid losses due to evaporation.

All food, refusals, and excreta were weighed on the same accurate pan balance to the nearest 0.1 Gm., with precautions to keep exposure to the air and to room temperature at a minimum. Amniotic fluid and blood lost at delivery were collected as completely as possible and weighed and analyzed. During the puerperium the breasts were pumped daily and all secretions saved for analysis. Perineal pads used in collecting lochia during the postpartum period were soaked in a measured amount of water, squeezed to remove soluble electrolytes, and analyzed for nitrogen and minerals. Water loss in the perineal pads was not measured and constitutes a source of error in calculations of water balance in the postpartum periods.

Urine was placed immediately after voiding in a jug containing 50 ml. of light mineral oil and kept refrigerated between additions, in order to prevent loss of ammonia or changes in pH and titratable acidity. Urine was analyzed daily for pH, specific gravity, titratable acidity, ammonia, nitrogen, sodium, potassium, chloride, calcium, and phosphorus. Analyses for pH, titratable acidity, and ammonia were completed within 24 hours after completion of each collection; the other analyses were completed within three days after the completion of collection. Water content was determined by drying, to constant weight, a measured amount, or aliquot, of each day's sample.

Diets, stools, and other solid materials were homogenized in a Waring Blendor, using a measured and recorded amount of water for dilution. This added water was later subtracted in calculating water content of the sample. For determination of water content, aliquots of 100 ml. in triplicate were measured into tared evaporating dishes, weighed again, and dried to constant weight in an oven at 58 to 60° C. Another portion of the homogenate was digested with 3 per cent by volume of concentrated sulfuric acid to form a mixture which could be bottled and stored for later analysis of nitrogen and electrolyte content.

Methods

I. Serum.—Sodium and potassium were determined by a flame photometer method using the Beckman DU Spectrophotometer with a Beckman 9200 Flame Attachment. Standards were prepared with sodium and potassium in the same proportion as they occur normally in blood. The reading of each unknown was compared to one standard reading slightly higher and another standard reading slightly lower, and the concentration of the unknown interpolated from these readings and concentrations.

Chloride was determined by the method of Schales and Schales[6]; calcium by the method of Kramer and Tisdall[7]; phosphorus by the method of Fiske and Subbarow[8] adapted to a spectrophotometer; blood urea nitrogen by a slight modification of the method of Van Slyke and Cope[9]; carbon dioxide content by a slight modification of the method of Van Slyke and Neill[10]; and plasma proteins with the use of the Howe precipitation of albumin, micro-Kjeldahl digestion, and nesslerization according to standard methods.[11]

II. Urine.—Sodium and potassium were determined by appropriate modifications, primarily in the dilution of the sample, of the blood method outlined above. Chloride was determined by the method of Schales and Schales[6]; calcium by a modification of the method of McCrudden[12]; phosphorus by the method of Fiske and Subbarow[8]; nitrogen by a micro-Kjeldahl procedure using selenium as a catalyst followed by distillation and titration of the ammonia[13]; titratable acidity by the method outlined in Hawk[11]; ammonia by a slight modification of the method of Van Slyke and Cullen[15]; and pH with the Beckman, Model G, pH Meter.

III. Stools and Diets.—Aliquots of the sulfuric acid digest of stools and diets were digested and ashed with a mixture of sulfuric, nitric, and perchloric acids.[16] The clear acid solution was diluted with water, neutralized with ammonia, and analyzed for calcium, phosphorus, sodium, and potassium according to methods described for urine. Nitrogen determinations were performed directly on the sulfuric acid digest by the procedure outlined for urine.[13] Chloride was determined on the fresh homogenate or on the sulfuric acid digest by a modification of the method of Wilson and Ball.[17]

Sodium

A. Results.—

The patient had been receiving a low-sodium diet, with an average intake of 32.6 meq. of sodium daily for six weeks prior to the metabolic study. During this interval, as we have already noted, she had developed hyponatremia on several occasions, to such degree as to necessitate the administration of sodium chloride on each occasion. The sodium balance, during this prestudy period, as calculated from the estimated sodium intake and the measured loss of sodium in the urine, had been markedly negative for most of this prolonged period. While a cumulative negative sodium balance of minus 46 meq. was determined from the calculated intake and the measured urinary output during the prebalance period between November 19 and December 1, the true extent of the sodium loss was accurately measured during the four-day period immediately preceding delivery.

With an analyzed daily intake of 34.1 meq. of sodium, the fecal loss was found to be small, averaging less than 5 per cent of the total excretion of sodium. On the other hand, the urinary loss was very large, resulting in a

mean negative balance of minus 18.5 meq. daily. The urinary sodium shows a decline during the four-day period of low salt administration. This decrease is not strictly progressive but the mean daily value for the four days is 50.5 meq. compared to 74.8 meq. for the two days of the prestudy period (Figs. 1 and 2). Daily urinary excretion on a "low-salt diet" had averaged 57.3 meq. during the previous four weeks of observation in the hospital.

Immediately post partum, on the same low intake of sodium urinary loss of sodium decreased sharply, amounting to only 10 per cent of the antepartum urinary sodium loss, resulting in a markedly positive balance. Even with the loss of over 9 meq. per day in perineal pads and breast milk, an average of 17.7 meq. of sodium, or 51 per cent of the sodium intake, was retained daily.

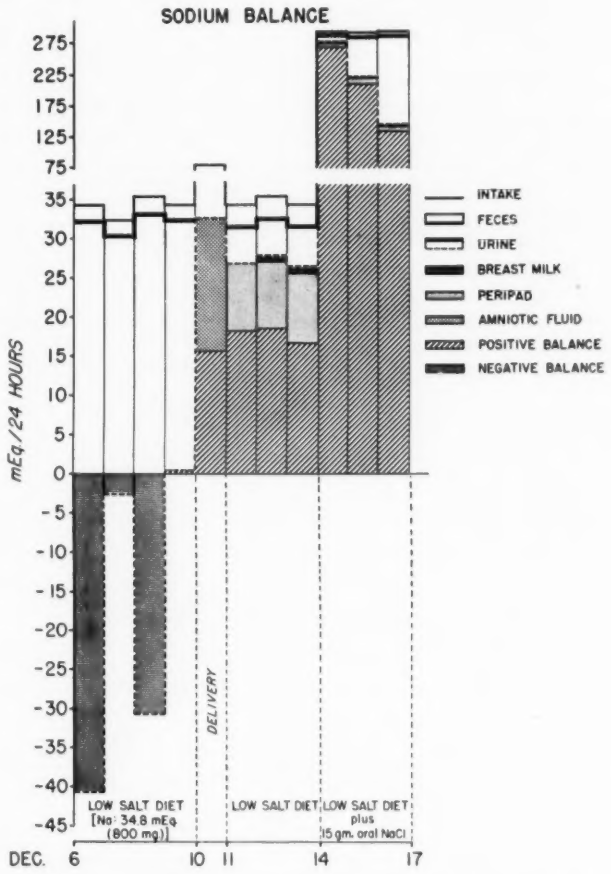

Fig. 1.—Daily sodium balance, calculated from the measured intake and considering the output in urine, feces, and other measured avenues of loss.

During the administration of 15 Gm. of sodium chloride (256 meq. sodium) orally, in addition to the dietary sodium, the positive balance increased sharply to very high levels. The mean retention of 70.9 per cent of the sodium intake for the three-day period is significantly higher than the 51 per cent of the intake on the low-salt diet. The response of the kidney to the increased sodium intake, however, was slow. On the first day of the increased intake of sodium (Fig. 2), the urine sodium increased only from 5 to 12 meq.; on the

TABLE II. SODIUM, POTASSIUM, AND CHLORIDE BALANCE

INVESTIGATOR	SUBJECT	PERIOD OF GESTATION	PERIOD OF STUDY (DAYS)	SODIUM (MEQ./DAY)		POTASSIUM (MEQ./DAY)		CHLORIDE (MEQ./DAY)	
				INTAKE	RETENTION	INTAKE	RETENTION	INTAKE	RETENTION
Hummel et al.[19]	Multipara	145 days—term	145	220	21.7	169	36	210	16.4
		10 days—term	10	202	10.8	165	28		
		10-53 days post partum	43	230	20.4	179	22.3		
Hummel et al.[20]	Primipara	65 days—term	65	120	4.7	104	0.4	107	-4.7
Coons et al.[21]	I	39 weeks	5	173	43.0	84	12.8		
	IV	39 weeks	5	316	76.4	113	17.4		
	V	38 weeks	5	210	78.6	86	19.5		
		39 weeks	5	201	27.8	81	10.2		
	VI	38 weeks	5	187	-5.6	86	12.3		
Freyberg[5]	Primipara	8 months—term	62		22*				
		Post partum	6		20*				
Thompson[4]	H. H.	8 months	11	145	11.6	107	10.4	166	1.2
	D. V.	Term	5	146	13.2	102	5.0	168	4.0
Authors	J. B.	Term	4	34.1	-18.4	78.4	14.1	35.5	-22.3
	(Mild pre-eclampsia)	Post partum	3	34.7	+17.7	78.7	9.5	40.1	-14.4
		Post partum	3	291.3	205.3	76.6	-18.2	296.8	151.3

*Figures read from charts, therefore only approximate.

second day it rose to 66 meq., while, on the third day, the urinary excretion rose to 151 meq. Upon returning to the low sodium intake alone, the urinary sodium excretion continued to rise for two days, to 196 and 295 meq. before showing a decrease reflecting the decreased intake, indicating approximately a 48-hour latent period in the response of the kidney to changes in sodium intake.

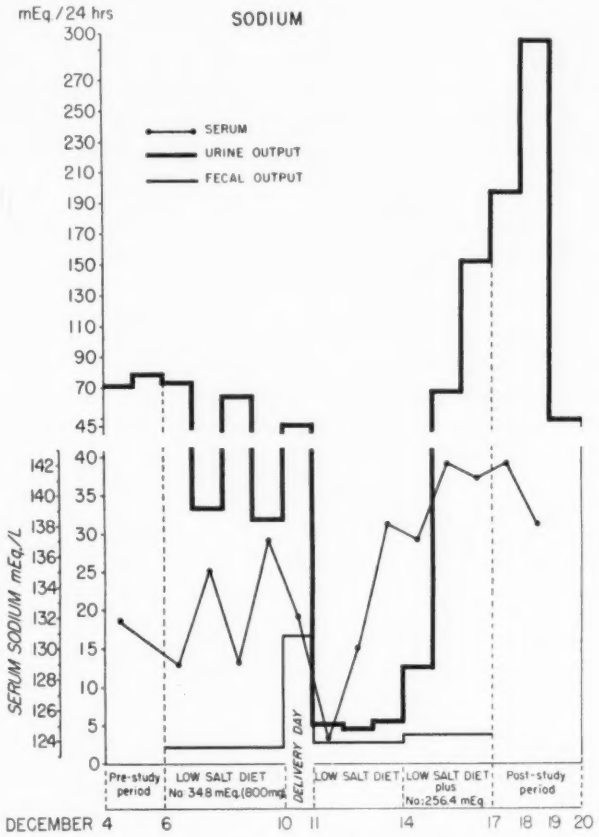

Fig. 2.—Serum sodium concentration in relation to urinary and fecal sodium excretion.

Changes in serum sodium seemed to be relatively independent of changes in urine sodium. Serum sodium values were somewhat erratic during the period immediately ante partum and always somewhat low, varying from 128 to 137 meq. per liter, substantiating the tendency to hyponatremia typical of this patient. On the first postpartum day, the serum sodium dropped to 124 meq. per liter, coinciding with the drop in urine sodium, a feature not infrequently noted by us in patients with pregnancy toxemia. Whereas the urine sodium remained low, the serum sodium returned in two days to 139 meq. per liter. With the increase in sodium intake, the serum sodium rose even higher, to 142 meq. per liter during the period of high urinary sodium excretion. It then declined slightly on the third day after the high sodium chloride intake was discontinued. Thus, in spite of the marked retention of sodium during the high sodium intake, the concentration of sodium in body fluids was maintained relatively constant, presumably by the increased reabsorption of water and expansion of the extracellular volume particularly in the interstitial areas.

B. Comment.—

The finding of a negative sodium balance at term in our patient is in sharp contrast to studies of sodium balance in normal pregnancy as reported in the literature. Most reports state that generally a retention of sodium occurs during the latter part of normal pregnancy.[18] Chesley[1] summarized the results of five investigators as we have previously noted. The mean sodium retention found by these workers in late pregnancy was 3.85 Gm. per week, which would represent a gain of approximately 24 meq. per day. If all this sodium were osmotically active, approximately 1 L. of water per week would have to be added to the extracellular fluid to maintain osmotic pressure of the body fluids and would more than account for all the weight gained in pregnancy. Even though it seems that all this sodium is not osmotically active, certainly a large part of it must be.

Studies by Hummel and associates,[19, 20] Thompson and Pommerenke,[4] Freyberg and co-workers,[5] and Coons and her collaborators,[21] summarized in Table II, show a positive retention of sodium in all but one case ranging from 5 to 78 meq. per day during the last two months of pregnancy. These positive retentions were obtained with patients receiving intakes of 100 to 300 meq. daily, in contrast to the intake of 34.1 meq. for our patient. This difference in intake may well account for the negative balance in our patient.

Likewise the change from a negative balance to a strongly positive balance post partum in our patient is contrary to the findings of others. The subjects studied by Hummel[19] and Freyberg[5] remained in positive balance post partum, but Taylor and co-workers[22] found significant decreases in sodium balance after delivery, to levels approaching equilibrium or negative balance, coinciding with the drop in urinary estrogen and pregnanediol concentration. These authors believe that the high level of sex steroids, especially the estrogens, in the body during pregnancy is one of the causes for the retention of sodium. With removal of the placenta and decrease in steroid-hormone concentration, the sodium retention decreases.

One might also postulate an increase in the activity of the sodium-retaining hormone of the adrenal cortex (or of the placenta) to explain the usual finding of sodium retention during late pregnancy, followed by decreased sodium retention post partum. In order to explain the findings in our patient which are so contrary to the usually accepted findings, where we note a precipitous drop in urinary sodium post partum, one would have to speculate upon the influence of the clinical condition of mild pre-eclampsia in altering the pattern usually seen in normal women. It might also be suggested that the decreased intake of sodium may exert an inhibitory influence on the output of steroids to explain the phenomena in our patient.

Gamble[23] found that the adjustment of the body to an increased intake of electrolytes is a slow process. The addition of 5 Gm. of sodium chloride to a normal constant dietary intake of sodium chloride resulted in an increase in sodium retention, followed by a decrease in retention as the surplus sodium was removed. In his study, body weight also increased at first. A period of fifteen days was required for sodium balance and body weight to stabilize at the control level again. When the increase in electrolyte load was continued for seven days (in infants), a prolonged lag in adjustment of excretion to increased intake occurred.

The findings in our patient correspond with those of Gamble, in that only on the fourth day after the addition of sodium chloride to the diet (and actually on the day the intake was decreased to control levels) did outgo exceed intake and thereby begin removal of surplus electrolytes from the body. Since this mechanism for adjusting reabsorption from the glomerular filtrate

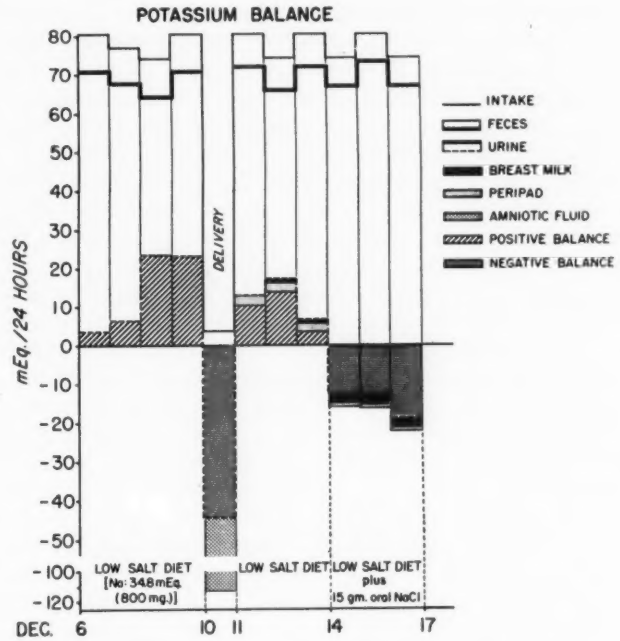

Fig. 3.—Daily potassium balance, calculated from the measured intake and considering the output in urine, feces, and other measured avenues of loss.

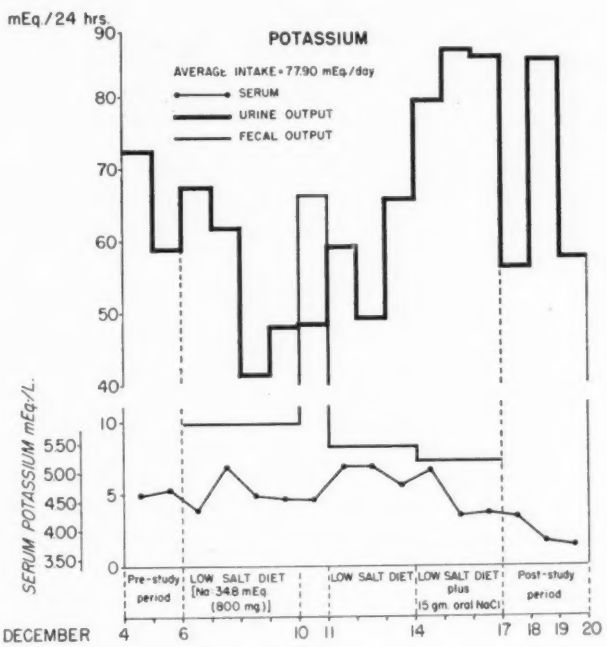

Fig. 4.—Serum potassium concentration in relation to urinary and fecal potassium excretion.

to the requirement for increased removal is so slow, it is well for the body that the increased rate of reabsorption of water is an immediate one, thereby maintaining the normal concentration of sodium in body fluids.

Another effect of the increased sodium load is that, with the increased sodium retention, the retention of potassium decreases.[23] This reciprocal relationship between sodium and potassium was first described by the German physiologist, Bunge. As shown in Table II, this relationship held true for our patient. With the addition of sodium chloride to the diet, the sodium retention increased from a mean of plus 17.7 to plus 205.3 meq. per day, and the potassium retention decreased from plus 9.5 to minus 18.1 meq. per day.

The decrease in serum sodium demonstrated by our patient post partum, followed by a gradual return to normal levels, might well be explained as being physiologic in origin, rather than related to changes in sodium intake. It might also be considered as the response to stress, increased work, and general body metabolism, or on the basis of mild acidosis during the immediate postpartum period. Goodland and associates[24] reported serial studies of serum sodium changes in four normal women receiving a normal diet for three to four weeks before and after delivery. They found a gradual decline to a low point of approximately 130 meq. per liter very close to the time of delivery (samples were not analyzed daily, so that the exact time of the minimum is not known), but they concluded that a significant rise to the level of 139 to 141 meq. per liter occurred during the first 10 to 15 days of the puerperium.

Bergstrom and Wallace,[2] to whom we have already referred, have found in rats that bone may serve as a reservoir for sodium and potassium, which can be quickly mobilized into the circulation when required by the body. The composition of the bone is not fixed, but reflects the state of chemical equilibrium in the body. It is possible that in cases of prolonged low sodium intake in the human, as in the rat, bone may contribute considerable quantities of sodium to the bodily economy and that conclusions based upon balance figures from dietary intake minus urinary and fecal losses might not be strictly accurate. Gamble also states that significant insensible loss of electrolytes occurs through the skin, which losses cannot be accurately determined in the balance studies as presently conducted.

Amniotic fluid probably should not figure in water and electrolyte balance studies inasmuch as there is no proof of osmotic exchange or of electrolyte or water exchange between amniotic fluid and the maternal circulation.

Potassium

A. Results.—

During the antepartum period on the low-salt diet, potassium balance was positive and became increasingly positive during the four days immediately before delivery, as a result of a progressive fall in the amount of potassium excreted in the urine (Fig. 3). On the low-sodium diet post partum, potassium balance remained positive, averaging approximately 10 meq. per day, in spite of small losses in perineal pads and breast milk, which totaled about 3 meq. daily. The fecal potassium loss was small, amounting to only 7 to 10 meq. per day, or 10 to 12 per cent of the intake. This loss remained about the same before and after delivery.

When the sodium intake was increased, the potassium balance became significantly negative, with an average daily loss from the body of 18 meq. during the three-day period. This negative balance was due primarily to a pronounced increase in urine potassium, from an average of 58 to 84 meq. daily. In order to be certain that the sodium chloride was not contaminated with potassium, it was analyzed for potassium and found to be free of this

electrolyte. Upon discontinuance of the high intake of salt the urine potassium showed no consistent pattern; it decreased on the first day, increased on the second day, and declined on the third day after the administration of high sodium chloride intake (Fig. 4).

Serum potassium levels varied between 4.5 and 5 meq. per liter, but showed no consistent trend, except for a tendency to decline when the patient was receiving the high salt intake. This decrease in serum potassium continued during the poststudy period to reach a low of 3.6 meq. per liter on the last day of her hospitalization.

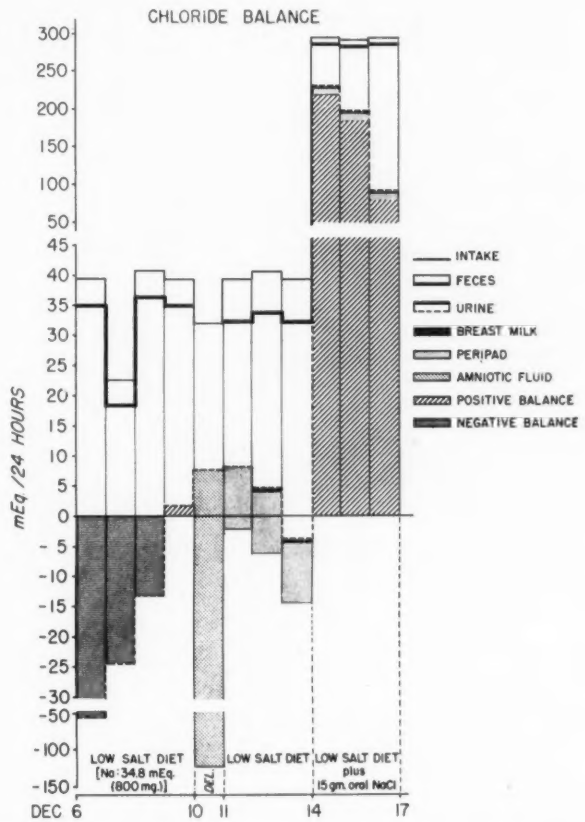

Fig. 5.—Daily chloride balance, calculated from the measured intake and considering the output in urine, feces, and other measured avenues of loss.

B. Comment.—

The potassium balance in our patient is comparable to results obtained by other investigators. Hummel[19] and Thompson[4] and Coons[21] report retentions varying from zero to 35 meq. per day during intakes of 80 to 175 meq. during the last two months of pregnancy, compared with the retention of 14 meq. daily for our patient receiving 78 meq. of potassium daily in the diet (see Table II). Hummel's patient remained in positive balance post partum as did our patient.

As previously discussed, the addition of large amounts of sodium chloride to the diet caused potassium retention to become significantly reduced, due to the marked increase in urinary potassium excretion. The increase in urine

potassium occurred immediately following the addition of sodium chloride, whereas the increase in urine sodium occurred gradually. It seems then that the kidney can adjust more quickly to changes in rate of reabsorption of potassium than of sodium. Apparently the decrease in reabsorption of potassium is so marked as to lower the serum concentration slightly, accounting for the low values during the "high-salt" period.

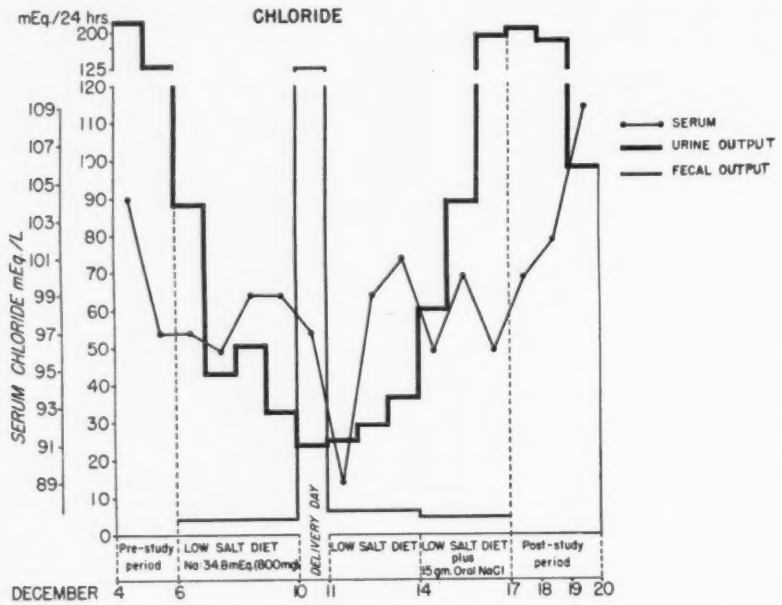

Fig. 6.—Serum chloride in relation to urinary and fecal chloride excretion.

Chloride

On the low-salt diet ante partum, the patient was in negative chloride balance. This negative balance became progressively less negative and finally positive on the last day just before delivery, due to the progressive fall in urine chloride excretion (Fig. 5). During the low-salt period post partum, the balance was slightly negative and the degree of negative balance increased each day as the urine chloride increased. The addition of 256 meq. of chloride as sodium chloride to the diet resulted in a strongly positive retention, which was slightly less positive each day due to the stepwise increase in urine chloride loss. The urine chloride remained high during the first two days after discontinuance of the additional salt (Fig. 6). This pattern of chloride excretion and balance closely resembles that demonstrated for sodium. Both electrolytes showed a delay in excretion after alterations in the quantity of electrolyte in the diet.

The serum chloride values were essentially normal during the antepartum period, with a mean value of 98 meq. per liter (Fig. 6). The value of 104 meq. on the first day of the prestudy period is somewhat high and may give a false impression of a gradually decreasing serum chloride level. A more accurate picture of the control level is obtained from the average value of 97 meq. per liter for the six days immediately prior to the metabolic study. On the first postpartum day, the serum chloride fell to 89 meq. per liter, coinciding with the sharp drop in serum sodium earlier noted. The serum chloride, however,

increased to antepartum levels on the second postpartum day and remained at the higher level with some daily fluctuations, until the high salt intake was discontinued. Then the serum chloride values increased progressively to reach a maximum of 109 meq. per liter on the last day of the study. No explanation for this rise is readily available.

Reports in the literature on chloride balance in pregnancy are few (Table II). Hummel's[19] multiparous patient, with a high intake of over 200 meq. of chloride daily, retained 16.4 meq. The primipara studied by the same group,[20] receiving one-half as much chloride in the diet, was in slightly negative balance. The two patients studied by Thompson[4] were essentially in equilibrium with a high intake. Therefore, it is not surprising that our patient was in negative balance with the very low chloride intake she was receiving.

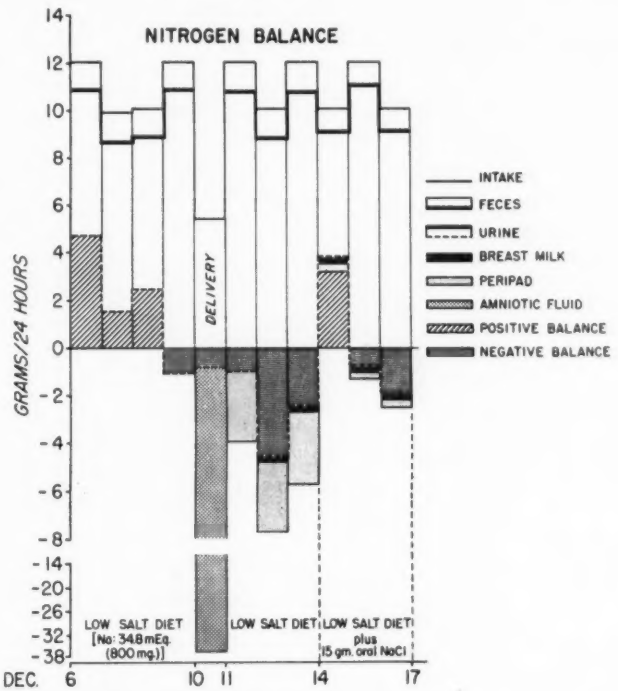

Fig. 7.—Daily nitrogen balance calculated from the measured intake and considering the output in urine, feces, and other measured avenues of loss.

Nitrogen

During the antepartum period the patient was in positive balance except for the last day immediately prior to delivery, when the urine nitrogen increased markedly and resulted in a negative balance of minus 1.0 Gm. (Fig. 7). The average daily retention for the four-day period was plus 1.94 Gm. A strongly positive balance is ordinarily expected because of the increased nitrogen requirement for building of fetal tissue and maternal viscera and adnexa. The average normal nitrogen retention during the last trimester of pregnancy is reported to be 2 to 6 Gm. a day.[25] This increase in nitrogen retention occurs as a result of a decrease in protein catabolism due to an economy in the expenditure of protein, similar to that which accompanies the processes of growth.

Post partum, the nitrogen balance remained negative during the first three-day period on the low-salt diet. The urine nitrogen continued to be high and the nitrogen loss in the perineal pads was considerable, averaging approximately 3 Gm. daily, thereby increasing the negative balance. According to studies reported in the literature, nitrogen balance regularly becomes negative during the puerperium. The report of Hunscher and her collaborators[26] of a multipara studied continuously during pregnancy, the puerperium, and lactation indicated a daily loss of 4.95 Gm. of nitrogen during the first nine days post partum, even with a dietary intake of 16.35 Gm. of nitrogen. This nitrogen loss, which probably reflects uterine involution and other tissue destruction during the postpartum period, cannot be checked by dietary measures.[25]

During the period of high salt intake, the nitrogen loss in the perineal pads decreased markedly, and even though the urinary nitrogen decreased sharply the first day, the increased output in the next two days resulted in a state of approximate equilibrium for the period.

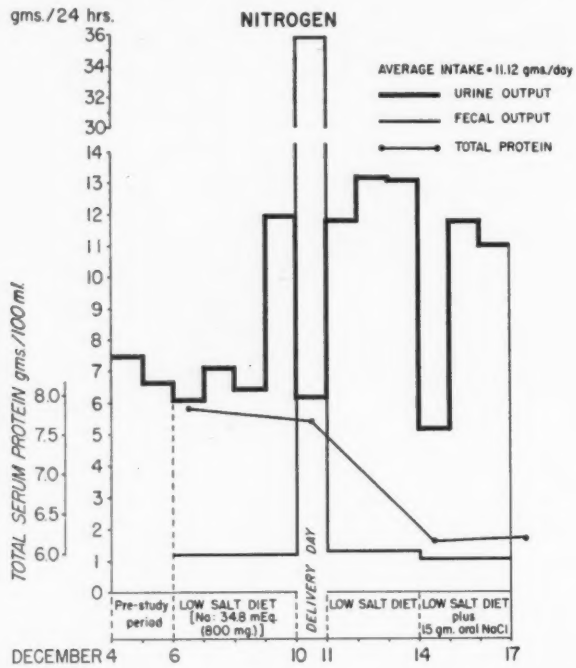

Fig. 8.—Total serum protein concentration in relation to urinary and fecal nitrogen excretion.

The serum protein values showed (Fig. 8) a significant decrease during the postpartum period; they decreased from 7.8 and 7.7 Gm. per 100 ml. to levels of 6.1 and 6.2 Gm. per 100 ml. This decrease was not altered by the increase in salt intake during the second period post partum. In studies reported in the literature, serum protein values decrease as pregnancy progresses. Part of the explanation for this decrease has been presumed to be the hydration known to occur in pregnancy. Coryell and co-workers[27] reported on a large series of patients showing that the total serum protein values were low during pregnancy but that they increased gradually over a 6 to 8 week period post partum. In our patient, a likely explanation for the marked decrease post partum seems to be the amount of blood lost at delivery. Instead of the expected de-

crease in blood hydration post partum, the hematocrit dropped from a predelivery level of 40 per cent to a postdelivery value of 30 per cent, and then to 27 per cent during the period of high salt intake. It seems plausible to assume that dilution of the blood, following blood loss, would account for the decrease in total serum protein.

Blood Nonprotein Nitrogen and Blood Urea Nitrogen.—

Accompanying the decrease in protein catabolism and the resulting increased nitrogen retention which occurs in normal pregnancy is a significant decrease in the nonprotein nitrogen of the blood. This decrease occurs primarily in the urea fraction. Normally the blood urea nitrogen may fall from 14 mg. to 6 mg. per 100 ml. during the first six months of pregnancy.[25] The blood urea nitrogen determination on our patient during the antepartum period was 8.5 per 100 ml.; it rose to 14.4 mg. on the day of delivery, remained slightly elevated at 13.2 mg. on the third day post partum, and then decreased to 7.9 mg. on the sixth day post partum during the high salt intake period. The nonprotein nitrogen also decreased from 37 mg. to 32 mg. per 100 ml. on the high salt intake; these changes also might be positively correlated with the decrease in hematocrit and with the hydration of blood produced by the retention of sodium and water during the period of high salt intake.

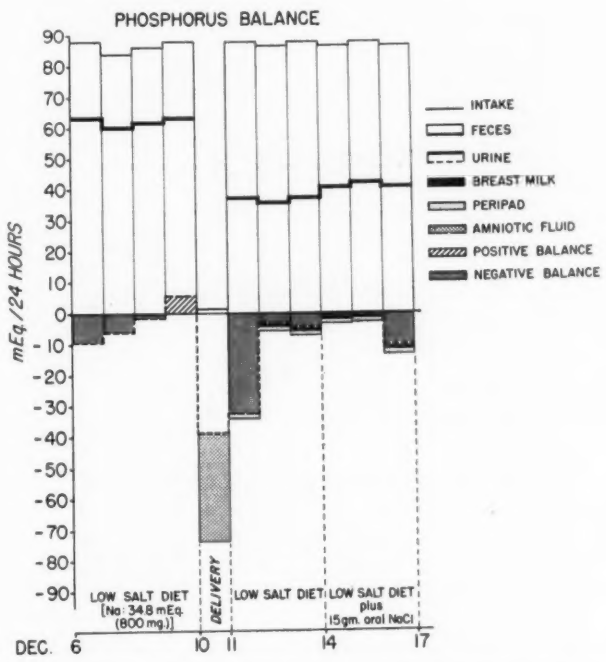

Fig. 9.—Daily phosphorus balance, calculated from the measured intake and considering the output in urine, feces, and other measured avenues of loss.

Phosphorus

During the antepartum period, the patient was essentially in phosphorus equilibrium, with a very slight negative retention during the first three days and a slightly positive retention on the last day of this period, while she was receiving an intake of 1.565 Gm. or 86.6 meq. of phosphorus daily (Fig. 9). The urinary loss of phosphorus averaged 73 per cent of the total excretion. The urinary loss also accounted for the excretion of 76 per cent of the phos-

phorus intake. These values are somewhat higher than the usual 60 per cent excretion of the intake in nonpregnant adults and the 52 per cent excretion reported in the literature for pregnant women in the last five weeks ante partum (Table III).

The phosphorus balance remained slightly negative after delivery; the losses of phosphorus in breast milk and the perineal pads were small and did not add significantly to the negative balance. The addition of large amounts of sodium chloride to the diet had no significant effect upon the phosphorus balance. The slight negative balance post partum might be anticipated because of the tissue breakdown which occurs during this period, with the accompanying loss of both phosphorus and nitrogen.

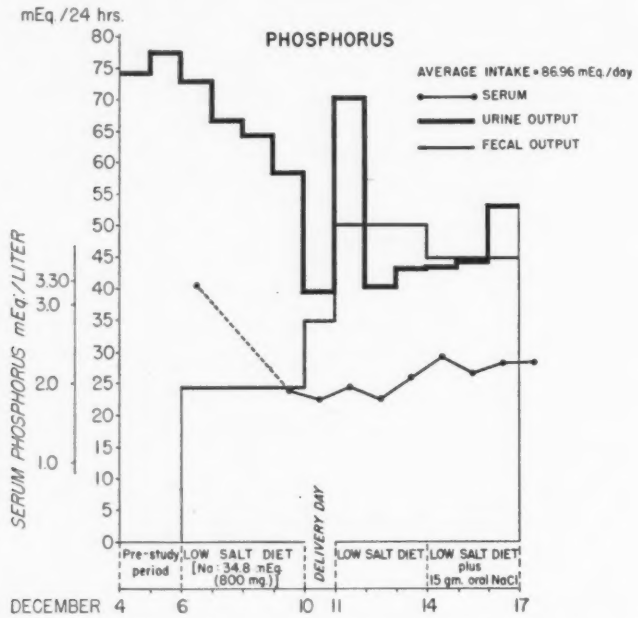

Fig. 10.—Serum phosphorus in relation to urinary and fecal phosphorus excretion.

Serum phosphorus values showed no significant changes with delivery. Fig. 10 shows a tendency toward a decrease in serum phosphorus during the low-sodium diet in the antepartum period, with maintenance of a low level post partum while on the low salt intake. A slight increase in serum phosphorus occurred on the high-salt diet, the significance of which is not understood.

The finding of a slightly negative retention of phosphorus during the antepartum period, in contrast to the strongly positive calcium and nitrogen balance, is difficult to explain. Phosphorus is utilized with calcium in the building of bone and with nitrogen in the building of body protein. Both these processes proceed at a greatly accelerated rate during the final month of gestation. One would expect parallelism between phosphorus and calcium particularly, and with nitrogen secondarily. Analysis of the data in the literature on calcium and phosphorus metabolism during pregnancy was attempted. In thirty-two studies of twenty-six women during the last four weeks of gestation reported in the literature (Table III), with the exception of two periods, these pregnant women were in strongly positive phosphorus balance. The mean retention was 19.9 per cent of the intake, which averaged 1.635 Gm. or 95 meq. per day.

TABLE III. CALCIUM AND PHOSPHORUS BALANCE IN LATE PREGNANCY

	CALCIUM				PHOSPHORUS			
	DAILY INTAKE (GM.)	URINE (PER CENT OF INTAKE)	FECES (PER CENT OF INTAKE)	RETENTION (PER CENT OF INTAKE)	DAILY INTAKE (GM.)	URINE (PER CENT OF INTAKE)	FECES (PER CENT OF INTAKE)	RETENTION (PER CENT OF INTAKE)
Mean of 32 studies on 26 women in last 5 weeks of gestation[19-21, 28-31]	1.589	16.8	59.5	27.6	1.632	52.0	30.6	19.9
Our patient, J. B., 6-0 days ante partum	1.74	7.5	40.2	52.2	1.565	75.7	27.9	-4.7

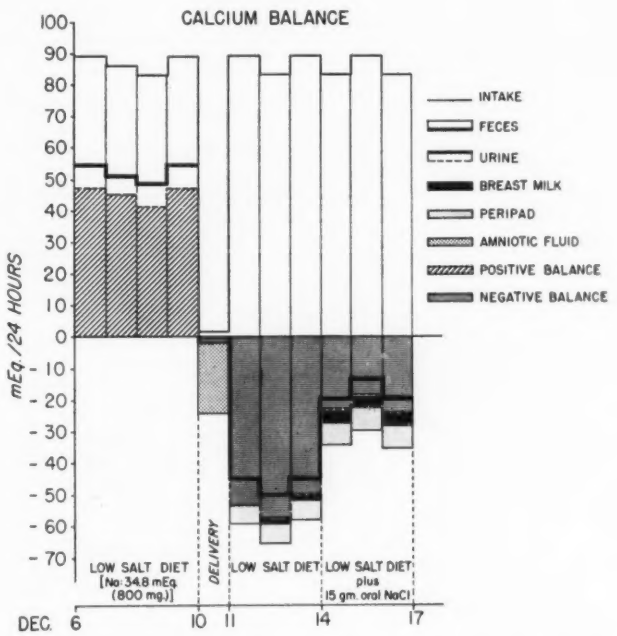

Fig. 11.—Daily calcium balance, calculated from the measured intake and considering the output in urine, feces, and other measured avenues of loss.

In one multipara studied during lactation by Hummel,[19] a negative phosphorus balance of minus 0.37 Gm. daily during the period 10 to 53 days post partum was found. These results are not strictly comparable to ours, however, since our patient in addition to the antepartum study was studied for only the first six days post partum. The negative retention at this time is anticipated from the tissue breakdown which is occurring, as we have already stated.

Calcium

During the antepartum period, the patient was in marked positive balance, retaining almost 50 meq. of calcium daily, or 52 per cent of the calcium intake (Fig. 11). The urinary calcium excretion was low; she excreted only 121 mg. (6.1 meq.) daily, or 7.5 per cent of the intake. The high retention agrees with findings on other subjects reported in the literature. However, the mean retention for twenty-six women in the last four to five weeks of gestation

(Table III) is only 27.6 per cent of the mean intake of 1.589 Gm. per day, compared to a retention of 52 per cent of the intake of 1.74 Gm. or 87 meq. per day for our patient.

Post partum, the fecal calcium loss was markedly increased during the first three-day period, resulting in a total negative balance of minus 60 meq. per day, when losses in perineal pads and breast milk are included. The urine calcium excretion showed little significant change post partum, although a slight increase occurred during the first two days of the puerperium. In subjects studied previously by one of us (E. K. S.)[32] and also confirmed by other workers, the urine calcium usually decreases sharply post partum to very low levels. In some patients, however, the decrease from the elevated levels typical of late pregnancy may occur as much as two to three weeks prior to delivery, with little further change following delivery. Our patient apparently belongs to the latter group. Since we have urine calcium determinations only during the last six days ante partum we cannot draw any conclusions as to the actual pattern for this patient.

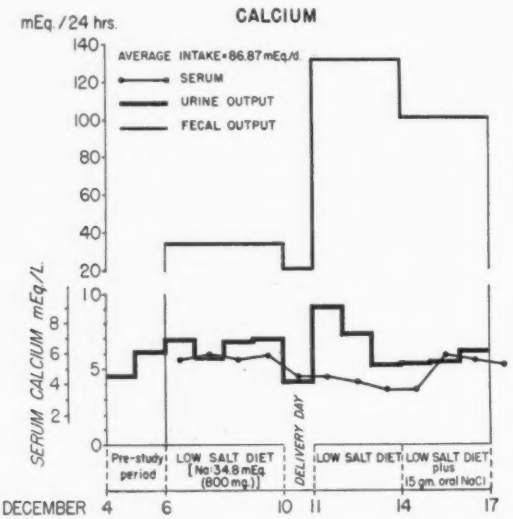

Fig. 12.—Serum calcium in relation to urinary and fecal calcium excretion.

The negative calcium retention in the postpartum period agrees with the findings of Hunscher and associates.[26] Although their patient was not studied during the immediate puerperium, but during days 10 to 53 post partum, she had a negative balance of 480 mg. (minus 24 meq.) daily. It appears from our findings that the administration of excess amounts of sodium chloride increased the absorption and retention of calcium, but the mechanism of this effect is obscure.

Serum calcium values declined on the day of delivery and remained low during the period of salt restriction in the puerperium (Fig. 12). These values then rose to antepartum levels during the period of high salt intake. It is debatable whether these changes relate directly to the changes in sodium chloride intake or whether they are merely physiologic. Bodansky[33] reported that serum calcium declines during pregnancy to a minimum value during the ninth month of pregnancy. The level rises toward normal at or slightly before labor and reaches normal levels within one to two weeks post partum. Changes in the hydration of the blood would not account for the increase in serum calcium in our patient because the hematocrit decreased rather than increased

during sodium chloride administration. It seems more likely, therefore, that the increase in serum calcium is physiologic in the immediate postpartum period.

The distribution of excretion of calcium and phosphorus between urine and feces in our patient varied considerably from the mean values taken from the literature (Table III). The urine calcium was low and the calcium retention particularly high. On the other hand, the urine phosphorus was markedly elevated above the mean, resulting in a slightly negative phosphorus balance. Whether this situation was of long duration or merely part of the immediate antepartum prodromal functional changes for this patient, we have no way of knowing.

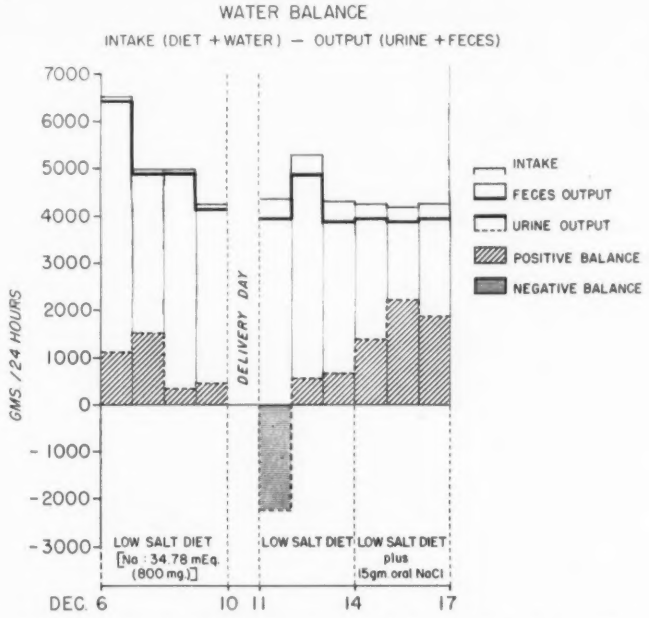

Fig. 13.—Daily water balance, considering only water intake in the diet and in drinking water, and water lost in urine and feces.

Water

A. Results.—

Water balance may be calculated in many ways. If one considers only water intake which is obvious in dietary fluid and in drinking water and then subtracts the water lost in urine and feces, results such as shown in Fig. 13 are obtained. During the four-day antepartum period on the low-sodium diet, the patient was in positive balance; that is, the patient was excreting less water than was being ingested. The water retention amounted to somewhat over 1,200 ml. daily during the first two days and decreased to approximately 400 ml. on the two days immediately prior to labor and delivery. This situation obtained in spite of the fact that the patient had been receiving the low-sodium diet for six weeks, with an essentially constant sodium and fluid intake. On the day following delivery, the patient experienced marked diuresis, supposedly typical for the postpartum patient, with excretion of approximately 2,200 ml. more water than was ingested. During the next two days the patient was in positive balance of approximately 600 ml. per day. (These figures do not include water losses in breast milk and lochia.) Finally, during the three days of high sodium chloride intake, the water balance was strongly positive, with a mean retention of almost 2,000 ml. daily.

TABLE IV. WATER EXCHANGE
(GM.)

DATE	BODY WEIGHT (KG.)	WATER OF DIET	WATER DRUNK	WATER OF OXIDATION	PRE-FORMED WATER	TOTAL WATER AVAILABLE	WATER OF URINE	WATER OF FECES	WATER IN BREAST MILK	WATER* VAPOR (INSENSIBLE)	TOTAL* WATER ELIMINATED	WATER* BALANCE
12-6	81.08	1,599.69	4,900	149.51	-42.4	6,606.8	5,142.2	68.16		1113.9	6,324.3	+282.5
7	80.97	1,363.90	3,590	110.06	-42.4	5,021.6	3,345.6	68.16		1113.9	4,527.7	+493.9
8	81.42	1,551.56	3,430	155.60	-42.4	5,094.7	4,575.9	68.16		1113.9	5,757.9	-663.2
9	80.74	1,599.69	2,640	149.51	-42.4	4,346.8	3,738.2	68.16		1113.9	4,920.3	-573.5
		1,528.71	3,640	141.17	-42.4	5,267.5	4,200.5	68.16		1113.9	5,382.6	-115.1
10						*Delivery Day*						
11	75.98	1,599.69	2,750	149.51	127.2	4,626.4	6,156.2	401.00		330.0	6,887.2	-2260.8
12	73.71	1,551.56	3,735	155.60	127.2	5,569.4	4,316.0	401.00	43.87	330.0	5,090.9	+478.5
13	73.94	1,599.69	2,715	149.51	127.2	4,591.4	3,252.9	401.00	43.87	330.0	4,027.8	+563.6
		1,583.64	3,067	151.54	127.2	4,929.1	4,575.0	401.00	43.87	330.0	5,335.3	-406.2
14	73.94	1,551.56	2,715	155.60	4.8	4,427.0	2,543.5	307.30	145.1	1139.9	4,135.8	+291.2
15	73.94	1,599.69	2,600	149.51	4.8	4,354.0	1,677.9	307.30	145.1	1139.9	3,270.2	+1083.8
16	75.64	1,551.56	2,700	155.60	4.8	4,411.9	2,091.8	307.30	145.1	1139.9	3,684.1	+727.8
		1,567.60	2,672	153.57	4.8	4,397.6	2,104.4	307.30	145.1	1139.9	3,696.7	+700.9
17	75.98		2,715				4,375†					
18	74.28		2,390				4,265†					
19	73.71		2,270				2,830†					

*Does not include water in lochia, therefore not strictly accurate.
†Values in milliliters instead of grams.

Water balance calculated in this manner ignores other important sources of water addition and water loss in body economy. Water formed in the oxidation of food, water gained or lost in the catabolism or anabolism of body tissue, and the insensible loss of water through vaporization from skin and lungs all must be included in considerations of total water balance. These avenues of water gain and loss are taken into account by proper calculations which have been worked out by Newburgh and his co-workers. Using the values obtained in our patient and calculating these data according to Wiley and Newburgh,[34] we obtain the results recorded in Table IV and Fig. 14.

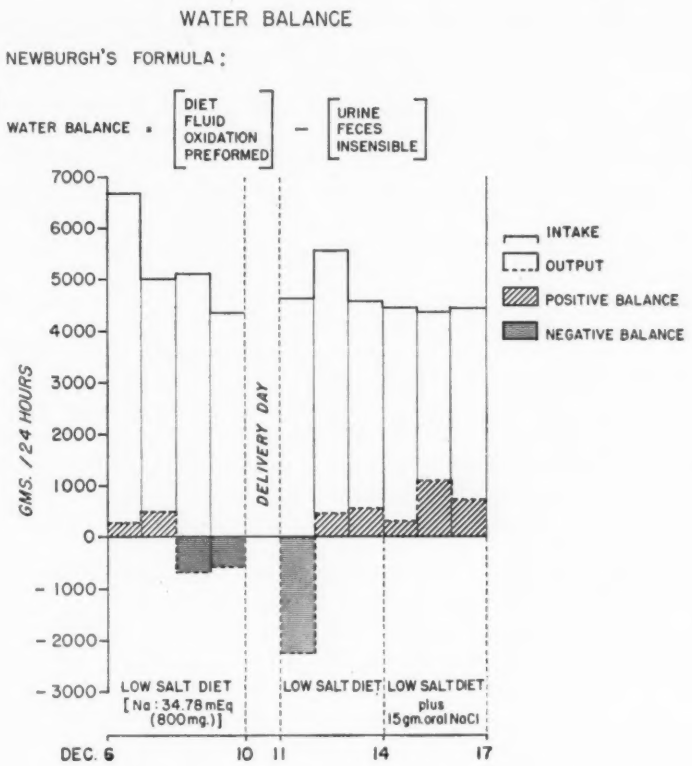

Fig. 14.—Daily water balance, considering all sources of water intake and all avenues of water loss according to Newburgh.[34]

The method of calculation of water balance, when all sources of water are considered, is depicted in Fig. 15, together with a sample calculation of one day's balance for our patient. To the sum of fluid water, the water of the diet, and the water of oxidation of foodstuffs is added or subtracted an amount of preformed water to determine total available water. Since preformed water is determined by the nitrogen balance, this water is added to the water intake if the nitrogen balance is negative and subtracted if the balance is positive. The use of the factor of 21.9 for lean body water in relation to nitrogen balance, as proposed by Moore and associates,[35] replaces the more cumbersome calculations of Newburgh. From the total available water is subtracted the sum of water of feces, of urine, and the insensible water to give the true water balance.

During the antepartum period the patient was approximately in water equilibrium, with a slightly negative mean balance of minus 115 ml. per day.

A glance at the daily changes, however, shows that the patient was in positive balance for the first two days, then went into negative water balance two days before delivery, with losses of approximately 600 ml. water daily.

Because of the technical difficulties involved in collecting all the amniotic fluid and blood lost at delivery, values for water balance on the day of delivery are not included in the table or figure. Since the lochia is not totally recoverable, the water lost in perineal pads also is not included in the calculations and the values for water balance during the puerperium are inaccurate by this unknown amount. Only the weight variations may be considered as accurate water balance in the postpartum patient.

On the first postpartum day a marked diuresis occurred, resulting in a negative water balance of minus 2,260 ml. The mean value for the postpartum low-salt period is minus 406 ml. per day, even though the water balance was positive by approximately 500 ml. on the second and third postpartum days. Institution of the high-salt diet caused retention of increased amounts of water sufficient to produce a mean retention of 701 ml. per day.

The increase in water retention is reflected in changes in urine volume and in body weight (Table IV). The urine volume decreased from a mean of 4,575 ml. during the low-salt period to 2,104 ml. during the high-salt period, or a mean decrease of 2,471 ml. per day. On discontinuance of the salt addition to the diet, the urine volume increased sharply, with no change in fluid intake. The urine volume was 4,375 ml. and 4,265 ml. on December 17 and 18, compared to 1,678 ml. and 2,092 ml. on December 15 and 16.

Weight changes correlated well with the water retention. Since weight measurements were taken before breakfast each morning, the body weight on the morning of December 17 is indicative of changes caused by the third day of high salt intake. After three days of high salt intake, the patient's weight rose from 73.94 to 75.98 kilograms, a gain of 2.04 kilograms. With return to the low-salt diet, the weight decreased promptly to 73.71 kilograms in two days, in association with the loss of excess water in the urine.

The specific gravity of the urine also increased significantly during the high salt intake, reflecting both the decrease in volume and the increase in concentration of sodium and chloride electrolytes excreted.

Undoubtedly the increase in weight and decrease in urine volume result from the increased sodium retention which occurs on the high-salt diet. The sodium retention promotes an immediate increase in the reabsorption of water, with a resultant expansion of the extracellular fluid space in an effort to maintain the normal concentration of sodium in body fluids until other, slower adjustments to the increased intake can be made.[23] In our patient, however, the amount of water retained, 700 Gm. per day, was not proportional to the amount of extra sodium, 187 meq., retained during the sodium chloride supplementation. In order to dilute this amount of sodium to the concentration normally found in serum, 140 meq. per liter, 1,335 Gm. of water should have been retained. The most important adjustment to the increased intake is the increase in urinary excretion of sodium and chloride, in which we found a definite lag and which required about 48 hours to reach optimum efficiency. The increase in water retention accompanying the sodium retention and expansion of the extracellular fluid space undoubtedly is directly related to the development of edema in susceptible patients. No edema appeared in our patient, presumably because the high-salt regimen was not maintained long enough.

The insensible water loss was calculated according to the method of Newburgh,[34] based on the difference between the sum of the patient's initial body weight and the weight of all the food and liquid ingested and the sum of her final body weight and the weight of all the material excreted, plus the differ-

ence between the weights of carbon dioxide produced and oxygen absorbed in the oxidation of the metabolic mixture (diet). The figure for insensible loss in our patient during the antepartum period is 1,113.9 ml. per day, which is very close to the value of 1,000 ml. for insensible water ordinarily used in rough calculations of water balance.

The insensible water loss during the immediate postpartum period was calculated to be only 330 Gm. daily, whereas the value increased to 1,140 Gm. daily on addition of sodium chloride to the diet. Partial explanation for the low value probably lies in the excessively large postpartum stools, with accompanying increased loss of water. Newburgh[36] stated that the largest errors in water balance consistently occur on days when an unusually large stool is voided. Likewise Peters[37] stated that deviations from the average heat lost by vaporization (insensible water) occur frequently and unpredictably, and that "they are especially prone to occur when the water content of the body is abnormal or is rapidly altered." Certainly marked alterations in water content of the body are occurring at delivery and in the early puerperium, which could conceivably account for the unusual results obtained in our patient.

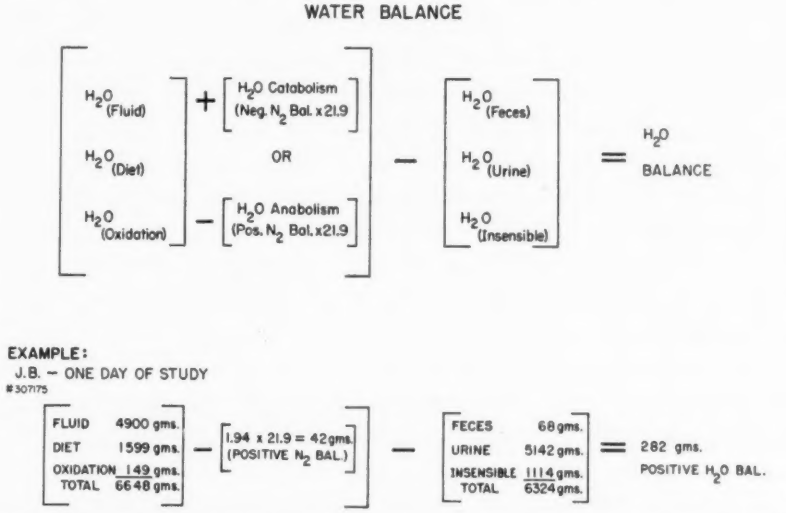

Fig. 15.—Illustration of the method of calculating water balance when considering intake from fluid, diet, water of oxidation, and preformed water, and output in feces, urine, and insensible water loss.

It is not possible, from this study, to determine the water requirement in pregnancy. Unfortunately, the complete water balance could not be measured for a long enough time before the patient went into labor, or before she began to show a spontaneous prelabor diuresis with development of a negative water balance.

B. Comment.—

The only study available in which actual water balance during pregnancy was measured, and to which our studies can be compared, is that of Freyberg and his associates.[5] These authors studied a healthy young primipara during the last sixty-two days of pregnancy and the first seven days post partum on a constant diet throughout except for five days of increased sodium intake immediately prior to delivery. Water balance was calculated according to the formulas of Wiley and Newburgh. The patient was in positive water balance

during most of the antepartum periods, 12 of the 17 three-day periods in which accurate balance could be obtained. The negative balance periods occurred each time when the body weight *decreased.*

The addition of 5 Gm. of sodium chloride to the diet during the last six days before delivery resulted in a positive balance of 1,000 Gm. of water the first three days, but a negative balance of minus 201 Gm. on the second three days immediately preceding delivery. This loss of water immediately ante partum is similar to the findings in our patient where a negative balance of minus 600 Gm. of water occurred on the two days immediately prior to onset of labor.

Freyberg's patient continued in negative water balance for two days immediately post partum, and attained a consistently positive balance on the fifth day of the puerperium; this trend is remarkably similar to that seen in our patient.

Summary and Conclusions

The complete metabolic balance of sodium, potassium, chloride, calcium, phosphorus, nitrogen, and water is presented in a patient with mild pre-eclampsia who had previously demonstrated a marked tendency to the development of hyponatremia on a restricted sodium chloride intake. The patient was studied for four days before delivery and three days after delivery while being maintained on a low-sodium diet, and for an additional three days when the diet was supplemented with 15 Gm. (256.4 meq.) of sodium chloride.

During the antepartum period, the patient was in negative balance for sodium and chloride, with correspondingly low serum sodium values. In spite of this loss of sodium from the body, simultaneous water retention occurred, i.e., she was in positive water balance, until two days before delivery when she underwent a spontaneous diuresis which resulted in a negative water balance of minus 600 ml. daily.

As expected, balances for the tissue-building elements, potassium, nitrogen, calcium, and phosphorus, were positive during the antepartum period. However, urinary nitrogen increased markedly on the day preceding delivery to a degree sufficient to evoke negative nitrogen balance.

On the same low-sodium diet, but during the postpartum period, the sodium balance became strongly positive, due to a marked reduction in the urinary sodium loss. The serum sodium decreased sharply to 124 meq. per liter immediately post partum, but spontaneously increased to normal levels in three days without augmentation of the sodium intake. Precipitous drops in serum sodium concentration, accompanying the stress of delivery, have been repeatedly noted by us, not only in the pre-eclamptic patient, but in the normal patient as well, with or without sodium limitation. Similar trends were demonstrated for chloride, although the decrease in urine chloride was not sufficient to bring about positive chloride balance. Serum chloride likewise decreased sharply on the day following delivery, then increased to normal.

Water balance on the day following delivery was markedly negative, probably due to a physiologic postpartum diuresis. This effect was temporary, however, with water balance being maintained at a slightly positive level from the second postpartum day to the conclusion of the study.

Potassium balance remained positive during the immediate postpartum period on the low-salt diet, although somewhat less positive than ante partum. Nitrogen, phosphorus, and calcium balances were negative. While the loss of nitrogen and phosphorus can be attributed to tissue catabolism, the excessive loss of calcium is not readily explained.

The addition of 15 Gm. of sodium chloride to the diet resulted in the retention of sodium and chloride in very large amounts during the three days of supplementation. The renal response to the increased intake was rather slow, requiring two days before urinary sodium and chloride excretion had increased to a degree sufficient to provoke removal of excess salt from the body. Nevertheless, serum sodium and serum chloride values increased only slightly and in neither instance did they exceed normal limits.

Water retention occurred, resulting in an increasingly positive water balance, probably to dilute the excess sodium and to maintain homeostasis of the extracellular fluid. The retention of water was not proportional to the amount of sodium retained, however. The increased body weight and decreased urine volume reflected this increased water retention; these changes, however, were reversed on withdrawal of the dietary sodium chloride augmentation.

The high sodium chloride intake caused a pronounced increase in urinary potassium, with resulting negative potassium balance, and slight reduction in serum potassium levels. The negative balances for nitrogen, calcium, and phosphorus were reduced somewhat during the sodium chloride addition, but whether these effects resulted from the sodium chloride or merely from physiologic adjustments during the puerperium cannot be stated. Values for both serum calcium and serum phosphorus tended to increase slightly.

Since the persistent hyponatremia corrected itself spontaneously post partum, even though the low sodium intake was maintained, one must suspect that delivery or the toxemia of pregnancy or the combination of the two contributed to the etiology of hyponatremia. However, the similarity of our findings regarding the effects of excessive sodium chloride intake upon water balance to those obtained by Freyberg in a normal pregnant patient seems to indicate that electrolyte metabolism in mild pre-eclampsia is altered in a manner similar to that in normal pregnancy and that the essential difference between the two conditions is only one of degree.

While it would be most desirable to have studied this patient for more prolonged periods ante partum and post partum, with many variations in dietary, water, and electrolyte intake, the limitations placed upon studies such as these by the patient, facilities, and economy precluded more complete evaluation of our patient.

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THE EFFECT OF UTERINE STRETCH ON THE CLEARANCE OF p-AMINOHIPPURIC ACID IN THE DOG

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IN THE rabbit a number of traumatic stimuli give rise to extreme vasoconstriction in cortical nephrons, whereas blood flow through juxtamedullary nephrons is unimpaired and probably increased.[1] This shunt, with its attending cortical ischemia, has been invoked to explain a wide variety of clinical entities in man, but experiments with both dog and man have thus far failed to provide unequivocal proof for its functional existence in these species.[2] Recently, Sophian[3] has postulated that renal cortical ischemia may be the major etiological factor in toxemias of pregnancy. This concept considers resistance of the uterus to stretch as the cause of renal cortical ischemia via a "utero-renal reflex," subsequent to which the ischemic cortex elaborates a vasopressor agent. For its validity the theory relies solely upon the observation that, in the rabbit, stretch of the uterus is followed by visible blanching of the surface of the kidney.[4] In view of the noteworthy vasomotor instability of the rabbit,[2] the following experiments were performed on dogs in order to assess the changes in renal hemodynamics associated with uterine stimulation and to test the specificity of such a response.

Procedure

Nine mongrel female dogs were studied in the anesthetized state. In experiments requiring surgery thiopental sodium was the anesthetic; in all other experiments α-chloralose was used to avoid the hazards of prolonged thiopental sodium anesthesia and because it is preferable in renal function studies.[5] Food and water were withdrawn from the animal cages 15 hours prior to the experiments. Following administration of the anesthesia, a water load of 75 to 100 ml. per kilogram was given by stomach tube to insure adequate urine flow. The p-aminohippuric acid clearance (C_{PAH}) was used to measure effective renal plasma flow and the exogenous creatinine clearance (C_{Cr}) to estimate the rate of glomerular filtration. PAH was determined by the method of Smith[6] and creatinine by the method of Bonsnes and Taussky.[7] In other respects the clearance techniques were standard.

Following three to six control urine collection periods, renal hemodynamics were determined under the following variations of protocol:

1. Uterine Insufflation by the Abdominal Route.—In four dogs the abdomen was opened through a midline incision, both tubes ligated, and the anterior vagina entered. A polyethylene catheter was threaded through the cervix, and, by means of a syringe, the uterus was insufflated with air at sufficient pressure to distend it to two or three times its resting size.

2. Uterine Insufflation by the Vaginal Route.—In two dogs, 8 to 14 weeks after ligation of the cornua, a polyethylene catheter was inserted through the vagina into the uterus. Insufflation was accomplished by depressing the plunger of a syringe filled with 20 ml. of air until a sharp increase in resistance was encountered, and the pressure was maintained throughout the experimental periods.

3. Vaginal Manipulation.—In three dogs the vagina was distended digitally and by means of a speculum, to simulate the stimulation attending uterine insufflation via the vaginal route.

4. Nonspecific Sensory Stimulation.—In three dogs the skin over various parts of the body was pinched sharply with forceps about 10 to 15 times per minute.

5. Effects of Anesthesia.—Two dogs, not included in the above groups, were studied under thiopental sodium anesthesia without undue manipulation. Similarly, the effects of prolonged α-chloralose anesthesia were studied in two instances.

The over-all duration of the experimental periods in all the variations of protocol was approximately comparable.

Results

Fig. 1 graphically portrays the results in terms of C_{PAH} in successive urine collection periods for illustrative experiments involving uterine stretch, vaginal manipulation, and skin stimulation. Also included in Fig. 1 is a representative experiment under α-chloralose anesthesia without undue manipulation. Three additional experiments, one with α-chloralose and two with thiopental sodium, gave results comparable to those shown in Fig. 1.

TABLE I. SUMMARY OF CHANGES IN C_{PAH} DURING UTERINE INSUFFLATION, VAGINAL MANIPULATION, AND SKIN STIMULATION

UTERINE INSUFFLATION		VAGINAL MANIPULATION		SKIN STIMULATION	
DOG* NO.	RATIO†	DOG NO.	RATIO†	DOG NO.	RATIO†
1 (s)	1.14	5	1.19	3	0.69
2 (s)	0.76	6	0.85	3	0.82
3 (s)	0.83	7	0.77	7	0.90
3 (v)	0.84			8	0.67
3 (v)	0.66				
4 (s)	0.78				
Over-all means	0.77‡		0.79§		0.76
S.D.‖	±0.09		±0.09		±0.11

*(s) signifies surgical approach, (v) vaginal approach.

†Values cited are the ratios of the mean value during the experimental periods to the mean value during the control period.

‡Over-all mean eliminating Dog No. 1.

§Over-all mean eliminating Dog No. 5.

‖Standard deviation calculated as $\sqrt{\frac{\Sigma d^2}{n-1}}$.

In Table I all experiments are collated by showing values for the ratio of the mean C_{PAH} during the experimental periods to the mean C_{PAH} during the control periods of that particular experiment. C_{PAH} was decreased in five of the six experiments involving uterine stretch, in two of the three where the vagina was manipulated, and in all where the skin was stimulated. In two experiments (dogs No. 1 and No. 5) the procedures were attended by an increased C_{PAH}. These two instances are not included in the statistical calculations since they would unfairly minimize the general trend shown by the

over-all picture. Physiologically, this exclusion is justified since sensory stimulation reduces effective renal plasma flow and has not yielded hyperemia.[2] The most likely explanation for the increase in these experiments is that some poorly controlled factor yielded abnormally low values during the control periods. Since one of the dogs was sacrificed at the termination of the experimental period and the other subsequently succumbed to acute hepatitis, experiments on these dogs could not be repeated.

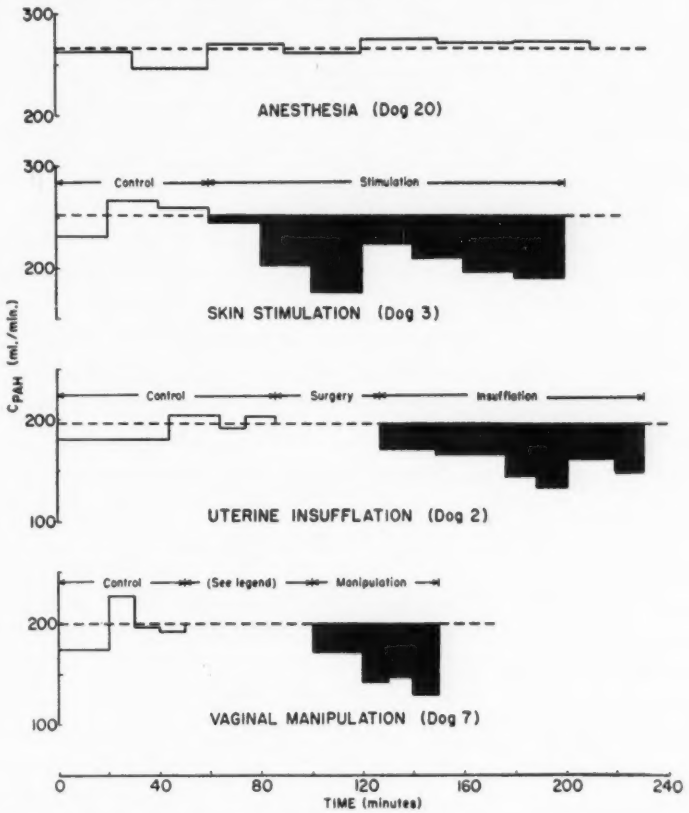

Fig. 1.—The effect of uterine insufflation and other stimuli on the clearance of p-aminohippuric acid (C_{PAH}) in the dog.

Each step line graph portrays a typical experiment for each variation of protocol.

The horizontal dotted line represents the mean of the control values.

No clearances are cited during the first 50 minutes of vaginal manipulation because of technical difficulties. Manipulation with a speculum proved difficult in this dog and occluded the bladder catheter with a consequent loss of urine around the catheter. To correct this difficulty digital manipulation was used in the latter part of the experiment.

Statistical analysis shows that C_{PAH} in successive control periods has a standard deviation of $\pm$ 9 per cent about the mean value. Under prolonged α-chloralose and thiopental sodium anesthesia the standard deviation is approximately the same as that during the control periods, indicating that duration and choice of anesthesia did not prejudice the data. Calculating the standard error of the difference between means and applying the t test shows that the mean reductions of C_{PAH} in Table I have a less than 1 per cent probability of being due to chance alone.*

*The standard error of the difference between means was calculated as $s_{m_d} = \sqrt{s_{m_c} + s_{m_e}}$; where $s_{m_c} = \frac{s_c}{\sqrt{n_c - 1}}$ for the control periods and $s_{m_e} = \frac{s_e}{\sqrt{n_e - 1}}$ for each of the experimental procedures treated separately.[3]

Changes in C_{Cr} were variable and inconsistent. Mean decreases of 1 per cent and 2 per cent were encountered in insufflation and skin stimulation, respectively. Vaginal manipulation was followed by a mean increase of 1 per cent.

Comment

Insufflation of the uterus brings about a modest reduction in C_{PAH}, and the data might be interpreted as favoring the theory proposed by Sophian. If his concept is correct that the kidney is etiologically involved in the toxemias of pregnancy, the renal response should be related solely to the uterus, i.e., involving a specific uterorenal reflex. Since vaginal manipulation and even a nonspecific stimulus such as skin pinching may produce decreases in C_{PAH} of the same magnitude as uterine insufflation, a specific uterorenal reflex seems unlikely.

The kidney is richly endowed with fibers from the sympathetic nervous system and renal blood flow is reduced by the hormones of the adrenal medulla. Since effective renal plasma flow is reduced in fright, pain, and psychoneurotic conflict,[2] all of which involve the sympathetic nervous system, it seems, therefore, that any stimulus of environmental circumstance having ultimate access to the sympathetic nervous system would reduce C_{PAH}. We favor this explanation of the reductions seen in our experiments.

The question remains as to the physiologic significance of a 23 per cent reduction in C_{PAH}. That C_{PAH} measures effective renal plasma flow under basal conditions is beyond dispute.[2] Admittedly, the technique loses reliability in certain conditions. For example, in oliguria unaccompanied by a true reduction of renal dynamics, the variability of clearances is greater because of bladder-emptying errors. Such a circumstance may be rejected in the present experiments because urine flow was at all times adequate to determine C_{PAH} within the variation previously cited. Alternatively, under pathologic conditions, such as the diuretic phase of acute renal failure where urine flow may be adequate, excretion of PAH may be so depressed because of either reduced renal blood flow or back diffusion, or both, that the error of measurement has the same order of magnitude as the value of the clearance. Since the standard deviation of C_{PAH} in control periods, under prolonged anesthesia, and in all experimental variations has the same order of magnitude, and since the standard deviation is one-tenth of the value of C_{PAH}, the latter alternative is also dismissed. Viewed in this light, Sophian's[3] categorical rejection of use of the clearance technique to demonstrate a uterorenal reflex is unwarranted.* The conclusion is inescapable that during uterine insufflation the renal parenchyma remained perfused by three-fourths of the blood supply in control periods.

Whether the 25 per cent reduction reflects increased flow of uncleared blood through the juxtamedullary circulation cannot be inferred in the present experiments in the absence of extraction ratios. Abundant evidence, as sum-

*Sophian's citation of Selkurt[9] is a spurious support of his rejection of the clearance technique. Selkurt's discussion concerned the insensitivity of the clearance technique to ascertain those fine variations of glomerular filtration rate which may participate in regulating sodium excretion. Selkurt's position in no way challenges the concept that effective renal plasma flow and filtration rate can be determined by the clearance techniques with an approximate error of ± 10 per cent under ordinary conditions.

marized by Smith, however, indicates that even more substantial depressions of C_{PAH} in the dog than here reported reflect a generalized renal vasoconstriction in which both the cortical and juxtamedullary circulations participate. It is concluded that sensory stimulation in the dog does not produce renal cortical ischemia such as Sophian and Franklin were able to obtain in the rabbit by uterine stretch.

Similarly, renal functional studies in man have shown no unequivocal evidence for a juxtamedullary shunt. Since the human circulation is more closely comparable to that of the dog than to that of the rabbit, participation of renal cortical ischemia in toxemias of pregnancy seems more remote than suggested by the experiments of Franklin and Sophian on the rabbit. It may be noted in passing that dog No. 3 was subjected to three experiments involving uterine insufflation and two with skin stimulation over a period of three months. Thirty days after the last such experiment her blood pressure is normal and her urine is free of protein. The possibility cannot be excluded, however, that the prolonged distension of the uterus in pregnancy and factors predisposing to pre-eclampsia-eclampsia (hypertension, Kimmelstiel-Wilson disease, diabetes, etc.) or combinations of these events may provide a more traumatic insult to the kidney than we were able to produce. Until such time as the renal functional impairment in pre-eclampsia-eclampsia shall be explained in terms of primacy of events, the role of renal cortical ischemia must remain conjecture.

Summary and Conclusions

1. In the dog, acute distention of the uterus induces a mean decrease of 23 per cent in the clearance of p-aminohippuric acid.

2. A similar reduction of the PAH clearance occurs during vaginal manipulation and skin stimulation.

3. In the dog, a specific uterorenal reflex appears improbable.

4. A summary of available evidence indicates that the above experimental procedures do not elicit renal cortical ischemia.

5. Renal cortical ischemia initiated by resistance of the uterus to stretch seems a remote possibility as an etiological factor in toxemias of pregnancy.

We are grateful to Dr. Edward L. Corey for helpful suggestions in pursuit of this investigation and to Dr. Herbert Jones for assistance in some experiments.

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THROMBOCYTOPENIC PURPURA RELATED TO THE INDUCTION OF LABOR*

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THE commonly accepted causes of hemorrhage in the postpartum period, though still existent, have in many large institutions been rendered practically harmless or eliminated. This progress has been achieved through a more thorough prenatal indoctrination, bringing a physically and emotionally well-prepared patient to delivery. At delivery, modern obstetrics has brought to the delivery room the realization that thorough, immediate, vaginal and often intrauterine examinations will disclose the cause of excessive blood loss and thus can result in prompt corrective measures. The greatest step forword, however, was made with the realization that blood must be available for immediate and intelligent use when hemorrhage occurs. There is still, however, a real danger when the atypical and unsuspected cause of hemorrhage is met. This can, by its very surprising nature, result in sudden massive hemorrhage and irreversible shock. Unusual causes when found must be publicized so that an awareness of them can be added to the armamentarium further to reduce the threat of hemorrhage to life.

The coexistence of thrombocytopenic purpura and pregnancy is not new in literature. Repeated cases have been reported[1] along with the methods of combating the purpuric condition. It is interesting to note that none of the cases reported were the result of pregnancy or the method of conducting labor. As will be seen in the review of the case presented, the causative factor was the development of a high degree of sensitivity to a very minute dose of quinine sulfate. A review of the literature disclosed only 42 cases of purpura which occurred concurrently with the administration of quinine. Purpura, therefore, occurring because of quinine must be considered relatively uncommon. In no instance was there a recorded case of a pregnant woman developing purpura when quinine was used for induction of labor or for any other purpose.

Purpura related to quinine medication was first described by Vipan[2] in 1865. Further reports in 1883 by Wigglesworth[3] and in 1897 by Montgomery[4] appeared in the *Boston Medical and Surgical Journal*. Rosenthal,[5] and Shrager and Kean[6] continued the report of cases. It was the latter who reported only 9 cases of purpura in 7,500 patients treated with quinine for therapy of ma-

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laria at Gorgas Hospital. This is a low incidence of 0.12 per cent. It was they who suggested that purpura was due to an allergic phenomenon and was not a simple toxic manifestation. Grandjean[7] showed by in vitro studies, using the plasma of the patient, that the platelet count was less in a normal sodium chloride solution saturated with quinine sulfate. Mamou[8] in 1947 reported anemia in addition to the thrombocytopenia. The literature[5, 6] contains evidence of the ability of quinine to influence the platelet count of a patient in selective instances. A case demonstrating this condition is reported.

Mrs. J. B., aged 23 years, gravida i, para 0, at term, was admitted to Milwaukee Hospital Maternity Pavilion on July 30, 1954, for the elective induction of labor. Her past history was noncontributory. Her initial prenatal physical examination, including chest x-ray and laboratory work, was negative. The prenatal course had been uncomplicated. All criteria justifying elective induction were present. (She was at term. The presentation was cephalic, engaged. The cervix was ripe, soft, somewhat effaced, and 2 cm. dilated.)

Examination on admission was negative. The induction was started 10:30 P.M. on July 30, 1954. Amniotomy was performed after a warm cleansing enema had been given. Quinine sulfate, 2 grains every half hour, was administered for three doses. Labor started shortly after the third dose, and delivery was effected under general anesthesia with the aid of a midline episiotomy and outlet forceps about four hours later, at 2:25 A.M., July 31, 1954. The female infant responded immediately. Medication used during labor consisted of Seconal sodium, 3¾ grains, 100 mg. of Demerol, and 150 mg. of scopolamine. The placenta was delivered immediately. The cervix and vault of the vagina were inspected before the episiotomy was repaired. Blood loss was minimal.

Within 25 minutes, while the episiotomy repair was being finished, a large hematoma developed in this area. Almost simultaneously, the area shaved for the obstetrical preparation was transformed into a mass of actively bleeding pinpoint hemorrhages. The drapes were removed and it was seen that the abdomen, the extremities, and all sites of pressure were covered with areas of ecchymosis. Bleeding from the vagina was minimal. The uterus was well contracted. The pulse and blood pressure were normal. In anticipation of an impending catastrophe due to some blood dyscrasia, blood was drawn for examination, glucose was started, and low-titer type O blood was requested to make blood available immediately and to eliminate the delay necessitated by cross matching. Medical and hematological consultation was obtained as soon as the consultants could arrive. (This was during the night.) During this short time interval the mucous membranes of the mouth began to bleed and signs of impending shock and vascular collapse were present. The blood pressure was 70/40, pulse was 144. A transfusion of 500 c.c. of low-titer O blood was administered. An immediate blood count showed 3.26 million red blood cells, 10.6 Gm. hemoglobin, and a thrombocytopenia of 57,000 platelets. A bleeding time of 2 minutes and a coagulation time of 10 minutes were recorded.

Drs. A. J. Quick of Marquette University School of Medicine and T. J. Greenwaldt of the Junior League Blood Center suggested the immediate intravenous administration of 300 c.c. of fresh frozen plasma. This was obtained from the Junior League Blood Center.

A 1 per cent solution of protamine sulfate in 500 c.c. physiologic saline was administered intravenously; 100 mg. of cortisone was given intramuscularly. Progressive ecchymosis stopped within one hour. Within several hours Dr. Quick confirmed the diagnosis of thrombocytopenic purpura. He reported that the prothrombin time, prothrombin consumption, and fibrinolysin determinations were normal, confirming the diagnosis of thrombocytopenic purpura.

On his suggestion protamine sulfate was discontinued, cortisone was continued, 75 mg. every 6 hours, and a unit of freshly drawn whole blood in plastic container was given for platelet transfusion.

When the patient's condition had stabilized, a review of the medical history showed no prior hemorrhagic tendency and no familial hemorrhagic diathesis. The historical point which became of greatest interest as the case progressed was that the patient had, some four years previously, ingested several Bromoquinine tablets for a mild upper respiratory infection, becoming acutely ill with nausea and vomiting several hours later.

By August 1, approximately 30 hours after onset, the patient appeared to be improving. She had an excellent urinary output and no evidence of additional purpuric areas. On August 2, further improvement was noted and some resolution of the large perineal hematoma was apparent. A Rumpel-Leede test was then negative, although thrombopenia persisted (53,000). Cortisone was reduced to 50 mg. every 8 hours.

On Oct. 8, 1954, approximately 2 months following the hospital discharge, the blood of this patient was studied by Miss W. Lutsey of the special Hematology Section of the clinical laboratory at Columbia Hospital. It was demonstrated (in vitro) that the patient's serum contained antibodies which, when the serum was mixed with a quinine saturated solution, would cause platelet agglutination and lysis, and an inhibition of clot retraction in the patient's blood and the blood of normal persons. In suitable controls, with the use of normal serum, such platelet destruction and secondary inhibition of clot retraction did not occur.

Another interesting feature of this case is the fact that the newborn, an otherwise normal infant girl, developed a rather severe thrombopenic purpura about six hours after birth. The baby was treated by Dr. P. S. Pierson with cortisone, resulting in an immediate response and an uneventful recovery. The infant's blood evidently contained antibodies from the mother by passage through the placental barrier. Situations such as this have been reported[9] associated with idiopathic thrombocytopenic purpura. Of 42 infants born to mothers afflicted with this type of purpura, only 15 survived.

Comment

The demonstration of specific antibodies in the blood of the patient with a history of quinine sensitivity seems to have confirmed the etiology of the acute, fulminating, thrombopenic purpura seen in this case. Not all of the laboratory criteria were satisfied, however. Typically, we might have expected prolongation of the bleeding time and clot retraction time in this case. Daily determinations of the bleeding time and clot retraction time did not exceed the normal values at any examination during the hospital course. Since blood clotting requires very few platelets, the blood coagulation time is usually normal in thrombopenic purpura, and was in our case on repeated determinations. The deficiency of thromboplastic substance in thrombopenia is usually disclosed by very low prothrombin consumption, but this test was reported by Dr. Quick as within normal limits. Leukocytosis, anemia (proportionate to the degree of blood loss from the vascular system), and thrombocytopenia, however, were clearly demonstrated and followed the expected trend with clinical recovery of the patient.

Treatment with cortisone was dramatic in the control of capillary fragility, the most important component of purpura. It is doubtful that the administration of a single unit of blood containing preserved platelets altered the course of the patient appreciably as there was no demonstrable rise in circulating thrombocytes some hours after this transfusion. At the time, however, the critical status of the patient seemed to warrant every possible therapeutic measure.

Of interest is the fact that hematological studies done April 26, 1955, nine months after the ingestion of quinine, showed quinine antibodies still present in the patient's blood. The patient could therefore easily be precipitated into another attack. To our knowledge the presence of antibodies at this late date has not been demonstrated in other cases.

The demonstrated effectiveness of cortisone therapy in this case of thrombocytopenic purpura is no more impressive in medical therapeutics than the finger of caution which this case directs toward intelligent conservatism in obstetrical procedures. This is especially indicated when one contemplates the elective induction of labor. Elective induction of labor is gradually gaining in popularity not only with the physician, obstetrician and general practitioner, but also with patients. The practical aspect and apparent safety of this procedure must be conceded in most instances where all criteria are fulfilled. The experience recorded in this case, however, demonstrates the fact that with all cautions exercised the unexpected can occur and stresses the great responsibility heaped upon the operator who undertakes an elective induction of labor. Where indications for induction are present, this responsibility is eliminated, for the need justifies the risk. Regardless of method, amniotomy or medication, even with the benign controversial quinine in minute dosage, complications can and will occur and this must be fully realized and anticipated by the physician who would take the risk. The prolapsed cord, the sudden alteration of fetal heartbeat, the sudden massive hemorrhage, the sudden intense labor resulting in cervical lacerations and at times a ruptured uterus are not new as complications. Now our attention is directed to violent, catastrophic, and almost fatal sensitivity resulting from quinine used as an agent for inducing labor.

Another word of warning must be sounded regarding the risks and responsibilities which devolve upon the physician choosing this procedure. It will take much explanation to convince parents and especially grandparents that abnormalities of infants born after induction are not the result of the procedure. In a recent experience in our practice a patient though unsolicited spontaneously refused induction to terminate her third pregnancy, since the previous infant had a troublesome feeding problem and the pediatrician had meekly suggested that induction might have been a factor. Therefore the unsuggested though mentally contemplated induction was pigeonholed with the outburst against induction. The third infant was born following spontaneous rupture of the membranes and after three hours of intense labor. A spontaneous laceration of the cervix secondary to this intense and rapid labor resulted in massive hemorrhage which required multiple transfusions. The obstetrician would have been in an unpopular and precarious position had he insisted that the contemplated elective induction by amniotomy be carried out in spite of the patient's firm stand against it.

Summary and Conclusions

A case, the first of its kind, of thrombocytopenic purpura in a pregnant patient secondary to the induction of labor is reported.

The causative agent was determined as being quinine sulfate which had been administered in minute doses.

Cortisone was demonstrated as an effective agent of therapy in thrombocytopenic purpura.

Emphasis is directed toward the responsibilities assumed by the physician who institutes labor by elective induction, regardless of the method used.

We are deeply grateful to Dr. A. J. Quick for his intense interest and helpful suggestions in managing this case.

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PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA*

A Review of 306 Cases

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PREMATURE separation of the normally implanted placenta is one of the gravest of obstetric emergencies with formidable maternal and fetal morbidity and mortality rates. There is consequently need for continued accumulation of pertinent information concerning this abnormality.

We have studied the obstetric records of the cases of premature separation of the normally implanted placenta for the period 1939 to 1950. The incidence of premature separation, age and parity, gestation period, degree of separation, incidence and effects of toxemia, type of therapy employed, and fetal and maternal mortality were reviewed.

Among the 72,207 women delivered during this period, premature separation occurred in 306, an incidence of 0.42 per cent. This figure closely approximates that reported recently by Bieber,[1] who found an incidence of 0.4 per cent (353 premature separations) among 79,972 deliveries at Charity Hospital, New Orleans.

Age of Mother, Gestation Period, Parity

Approximately 50 per cent of the 306 patients were between 20 and 29 years of age; 21 per cent were younger; and 28 per cent were older. It must be remembered, however, that among the 72,207 pregnancies the greatest number occurred in the 20-29 year age group, and, therefore, a greater number of complications was to be expected by virtue of numbers.

The period of gestation varied from 24 to 40 weeks. Sixteen per cent of the cases occurred between the twenty-fourth and twenty-seventh weeks of gestation; approximately 42 per cent occurred between the twenty-eighth and thirty-seventh weeks; and a similar percentage occurred between the twenty-eighth and fortieth weeks of gestation. Sixty-seven and eight-tenths per cent of the mothers were multigravidas.

Degree of Separation.—The degree of separation was classified as "mild," "moderate," or "severe," according to the classification of Sexton and associates.[2] Their Table V gives the following:

CRITERIA USED FOR CLASSIFYING DEGREES OF PLACENTAL SEPARATION

A. Mild.—

Pathological examination: 1/6 placental surface involved. No evidence of concealed hemorrhage. Less than 400 c.c. external bleeding.

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*Presented at a meeting of the Chicago Gynecological Society, May 20, 1955.

B. Moderate.—

Pathological examination: moderate amount of retroplacental blood; over ⅙ but less than ⅔ of placenta involved.
External bleeding over 400 c.c.
Tense but not boardlike abdomen.

C. Severe.—

Pathological examination: large amount of retroplacental blood; almost complete or complete involvement of placenta.
Usually external bleeding of slight to moderate amount. Larger amount concealed hemorrhage.
Uterus tense, tender, boardlike.
Varying degrees of shock.

Of the 306 patients, separation was mild in 158 (51.6 per cent), moderate in 50 (16.3 per cent), and severe in 98 (32.1 per cent).

Toxemia.—Toxemia, according to the classification recommended by the American Committee on Maternal Welfare, was found to have been present in 100 patients, or in one in three.

Toxemia was mild in 38 patients, severe in 60, and eclampsia occurred in 2. Severe separation was present in 15 (39.4 per cent) of the 38 patients with mild toxemia, in 32 (53.3 per cent) of the 60 patients with severe toxemia, and in both of the patients with eclampsia.

The mortality rate among the infants delivered from toxemic mothers totaled 68 per cent, compared with 49 per cent among infants delivered from nontoxemic mothers.

The number of premature infants increased with the severity of toxemia and degree of separation.

Infant Mortality.—The 306 mothers delivered a total of 310 infants, or whom 117 (37.7 per cent) were dead when the mother was admitted to the hospital. Nineteen (6.1 per cent) infants died during labor, and 35 (11.3 per cent) died after delivery. Survivors totaled 139 (44.8 per cent).

TABLE I. FATE OF 310 INFANTS BORN TO MOTHERS WITH PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA

	NO.	%
Fate of All Infants.—		
Dead on admission	117	37.7
Nonviable (under 1,000 grams)	16	5.2
Viable	177	57.1
	310	100.0
Fate of Viable Infants.—		
Died		
(14 between 1,000-1,500 grams 11 between 1,500-2,500 grams)	38	21.5
Survived	139	78.5
	177	100.0

Of the 310 infants, 179 (57.7 per cent) weighed less than 2,500 grams and were, therefore, classed as premature. Of the 19 (6.1 per cent) who died during labor, 10 were premature and 3 of these weighed less than 1,000 grams—the birth weight below which viability is usually not expected. Of the 35 infants who died neonatally, 31 were premature and 13 of these weighed less than 1,000 grams.

Elimination of the infants who died before the onset of labor (fetal heart tones were absent on admission) and those of a nonviable weight (less than 1,000 grams) leaves a total of 177 viable infants who were theoretically salvageable. One hundred and thirty-nine (78.5 per cent) survived, 38 (21.5 per cent) died (Table I). Of the 38 who did not survive, 14 weighed between 1,000 and 1,500 grams, and 11 weighed between 1,500 and 2,500 grams.

Maternal Mortality.—Six maternal deaths were attributed to premature separation of the normally implanted placenta. The case histories are summarized briefly in the following case reports.

CASE 1.—1939. This patient died ten minutes after admission. Unfortunately, a postmortem examination could not be obtained. This was thought to be a case of severe premature separation of the placenta.

CASE 2.—1939. A primigravida, 18 years of age, was admitted at term, not in labor. The blood pressure was 158/112, and pulse rate 92 per minute. Albuminuria was 3 plus. Fetal heart sounds were absent. The uterus was "boardlike" and normal in size for the length of gestation.

Four hours after admission, a stillborn infant weighing 6 pounds, 5 ounces, was delivered by cesarean section. The placenta was completely separated and 500 to 600 c.c. of old, clotted blood was expelled from the uterine cavity. The patient went into shock during operation.

The blood pressure remained at 90/60. The red blood count dropped to 1.7 million; the hemoglobin totaled 30 per cent. Each attempt at replacement of blood was followed by chills, and 20 hours after operation the patient died. She was Type A and was given cross-matched Type O blood. The Rh factor was not being determined at that time.

Autopsy disclosed an intraperitoneal hematoma, postoperative in origin, at the lower border of the low cervical uterine incision; parenchymatous degeneration of the liver; old chronic nephrosclerosis; and pulmonary edema.

CASE 3.—1940. A 42-year-old para xii, gravida xviii, who had had no prenatal care, was admitted in severe shock with a moderate amount of vaginal bleeding. The temperature was 95.4° F., respirations 40 per minute, with no pulse, and no blood pressure obtainable. She was about 36 weeks pregnant. The uterus was firm and no fetal heart tones were audible. The patient was given intravenous fluids, sedation, and external heat but died 30 minutes after admission. Postmortem examination showed complete separation of the placenta.

CASE 4.—1940. A gravida iv, para iii, 33 years of age, was admitted in convulsions, the sixth such attack in 20 hours. Prenatal care had not been sought.

Examination showed a blood pressure of 156/100. Vaginal bleeding was copious and the cervix was completely dilated. No fetal heart tones were audible. A stillborn infant was immediately delivered. Delivery of the placenta was followed by large blood clots.

Laboratory studies showed 4 plus albuminuria with many casts; a red cell count of 1.8 million; hemoglobin 40 per cent. Nonprotein nitrogen 56 mg., creatinine 3.7 mg. per cent. Hypertonic dextrose solution, magnesium sulfate, and 500 c.c. of blood were administered.

The urinary output during the 24 hours post partum totaled 35 c.c. The patient died 32 hours after admission without regaining consciousness. Permission for postmortem examination was denied.

CASE 5.—1948. A multigravida, 24 years of age, 38 weeks pregnant, was admitted in labor. There had been no external evidence of bleeding. The woman reported that she had been well until the night before, when she fell from a ladder.

There had been no prenatal care. Her first pregnancy had been accompanied by toxemia and had been terminated by cesarean section; her second had been normal with vaginal delivery; the third and fourth had ended early with spontaneous abortion.

The abdomen was found to be tense and tender to palpation. No fetal heart sounds were audible. The blood pressure was 110/20. On vaginal examination, the cervix was found to be 6 cm. dilated with breech presentation.

The membranes were artificially ruptured. There was no visible, active bleeding. After one hour of labor in the hospital, an infant was delivered by double footling breech presentation. Postpartum hemorrhage necessitated manual delivery of the placenta which was followed by large blood clots.

Uterine hemorrhage continued, with bleeding through a uterine packing despite the administration of oxytocics. Hysterectomy was performed one hour post partum, with the patient in profound shock. Whole blood and supportive therapy were administered to which the patient ultimately responded. On the first day postpartum, however, lower nephron nephrosis developed, and, despite the use of an "artificial kidney," the patient died three days later.

CASE 6.—1950. A primigravida, 28 years of age, was admitted in active labor and at term. No prenatal record was available. Examination disclosed irregular uterine contraction. No fetal heart tones were audible. The blood pressure was 160/100.

Vaginal bleeding began nine hours after admission. Vaginal examination failed to show palpable placental tissue. The membranes were artificially ruptured and 1 minim of Pituitrin was administered subcutaneously every 20 minutes. Blood transfusions and oxygen also were administered.

Delivery of a stillborn infant took place spontaneously after a labor of nearly 15 hours. Total separation of the placenta, with depression of cotyledons, was noted on completion of the third stage.

Hemorrhage immediately post partum resulted in the loss of approximately 1,600 c.c. of blood, following which bleeding continued through a uterine packing. The patient remained in shock although she received a total of 3,500 c.c. of blood. Hysterectomy was performed within one hour after delivery, but the patient died one hour after operation.

A study of these case reports of the maternal deaths indicates the lack of knowledge and facilities for adequate blood replacement in the earlier years of this report. There was little if any knowledge concerning fibrinogenemia and its treatment as we know it today. It is quite evident that adequate prenatal care would have prevented most of the maternal deaths.

Therapy.—During the twelve-year period covered by this review, no rigid plan of therapy for premature separation of the placenta was followed, inasmuch as the therapy for each patient was directed by one of six members of the attending staff whose ideas varied. In addition, as the years have progressed, certain ideas have been discarded and new ideas have been introduced. As a general rule, however, certain principles were followed. Blood loss or shock was treated by prompt blood replacement, and toxemia, if present, was treated with sedation, hypertonic glucose, and magnesium sulfate solutions.

The management of premature separation was by vaginal or abdominal delivery. Therapy with vaginal delivery was further divided into two groups, expectant or active.

By expectant therapy, we refer to the careful observation of the patient without any definitive action by the obstetrician. Expectant therapy was employed in the 104 patients (34.0 per cent) in whom (a) labor was in progress, (b) the maternal condition was good, (c) the condition of the fetus was either good or nonviable, and (d) usually, where replacement of blood was not indicated. Included in this group also were those patients in whom the membranes had ruptured spontaneously. Fifty per cent of the patients treated expectantly were in active labor.

Active vaginal therapy was employed in 165 patients (54.0 per cent). Approximately half of these patients were already in active labor.

Vaginal intervention consisted primarily of artificial rupture of the membranes (90 per cent). Willett's scalp traction was utilized in 8 cases, the Voorhees bag in 25, and Braxton Hicks version in 3 cases (the last 3 procedures being used less frequently in recent years).

Pituitrin was used in 11.1 per cent of all cases of premature separation during the two-year period, 1949-1950. It was usually used for induction of labor in the presence of ruptured membranes with a "ripe" cervix. We have been particularly impressed with the management of these patients. This will be the subject of a future presentation.

(The statistics thus far compiled on this new study show that, in 1951-1953, 104 instances of premature separation occurred in which only one patient was delivered by cesarean section and 20 were delivered with the use of a dilute intravenous Pitocin solution. There were no maternal deaths. This apparently indicates the recent trend toward fewer cesarean sections and the increase in the use of Pitocin at the Cook County Hospital.)

Cesarean section was employed in 37 instances (12.1 per cent). It was used: (1) in the presence of shock and/or persistent vaginal bleeding when delivery was not imminent; (2) where a completely damaged uterus was suspected; (3) in the presence of a normal, good-sized, living fetus when vaginal delivery was not anticipated in a reasonable length of time. Of the 37 cesarean sections performed, 6 required hysterectomy. Hysterectomy was performed twice following vaginal delivery because of uncontrolled hemorrhage.

Couvelaire Uterus.—Among the cases of severe separation, 14 instances of Couvelaire uterus were observed, an incidence of 37.8 per cent. We are sure that others could have been so classified had they been visualized at laparotomy. Of the patients who developed this condition, only 2 were toxemic. Six Couvelaire uteri developed with prematurely born infants, and the condition was associated with 4 of the 6 maternal deaths.

The distribution of types of therapy in relation to degree of placental separation is shown in Table II. It indicates that three times as many patients with severe separation were delivered vaginally as abdominally.

TABLE II. DISTRIBUTION OF TYPES OF THERAPY IN RELATION TO DEGREE OF PLACENTAL SEPARATION

TYPE OF THERAPY	NO.	%
Expectant	104	34.0
Separation mild		67.3
Separation moderate		14.4
Separation severe		18.3
Vaginal intervention	165	54.0
Separation mild		49.7
Separation moderate		16.4
Separation severe		33.9
Cesarean section	37	12.0
Separation mild		13.8
Separation moderate		22.4
Separation severe		63.8

Corrected Infant Mortality in Relation to Therapy.—When infant mortality figures are corrected by eliminating infants who were either dead before admission or who weighed less than 1,000 grams and did not survive, an "absolute" or "corrected" infant mortality figure can be computed for each type of therapy. Thus (Table III) it is found that the infant mortality rate was 18.9 per cent when vaginal intervention was employed; 24.3 per cent with expectant therapy; and 22.2 per cent with cesarean section.

TABLE III. THERAPY EMPLOYED AND FATE OF VIABLE INFANTS*

THERAPY	TOTAL INFANTS	MORTALITY						SURVIVAL	
		DIED INTRANATALLY		DIED NEONATALLY		TOTAL DIED			
		NO.	%	NO.	%	NO.	%	NO.	%
Expectant	70	8	11.4	9	12.9	17	24.3	53	75.7
Vaginal intervention	89	7	7.7	10	11.2	17	19.1	72	81.9
Cesarean section	18	1	5.5	3	16.6	4	22.2	14	77.8
Total	177	16		22		38		139	

*Infants who weighed 1,000 grams or more at birth, with fetal heart tones audible on admission.

Summary

1. Most obstetric patients with premature separation can be delivered vaginally without increasing the maternal mortality. Evaluation in retrospect of the maternal deaths at the Cook County Hospital offers no improvement in results if cesarean sections could have been utilized.

2. The infant mortality is not increased by vaginal delivery. Cesarean section does not ensure a living baby as evidenced by a 22.2 per cent neonatal fetal mortality.

3. Indications for cesarean sections were:

A. Maternal: (1) shock and/or persistent bleeding where vaginal delivery is not imminent. (2) cases where a completely damaged uterus is suspected.

B. Fetal: In the presence of a normal, good-sized, living fetus with vaginal delivery not anticipated in a reasonable length of time.

4. Toxemia of pregnancy occurred in one-third of the patients with premature separation. The incidence of prematurity increased with the presence of toxemia. The severity of the premature separation increased with the severity of the toxemia.

5. Pituitrin appears to be a valuable adjunct in the treatment of premature separation.

We wish to acknowledge the assistance and cooperation of Dr. William Powell Hutchinson.

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Discussion

DR. D. N. DANFORTH.—The authors' incidence of premature separation is within the usually reported limits. The maternal mortality and the fetal salvage as reported are not excessive for this extremely serious complication of pregnancy. These results are all the more remarkable, when one considers, first, the huge number of patients delivered in the ten-year period covered by this report, second, the fact that many of these patients had no prenatal care whatever and a large number made only sporadic visits, and, third, the very sizable training program which is involved in the care of these patients.

I agree entirely with the following points which are stressed by Dr. Daro: first, the necessity, for comparative purposes, of classifying these cases as mild, moderate, or

severe, precisely as outlined by Sexton. Second, the prompt and liberal use of blood transfusion in all of the severe cases, and in most of the moderate ones, in anticipation that many of the latter will become severe, and without warning. In this connection, it is becoming in some institutions increasingly fashionable to withhold transfusion in patients who are not approaching extremis, because of the risk of sensitizing to M, N, or Kell factors, or the like. In all obstetrical hemorrhages, and especially that of abruptio placentae, where the compensatory mechanisms may give way with great suddenness, it seems imperative that shock be anticipated and dealt with by liberal transfusion, and that the remote hazard of sensitization be disregarded. Third, I agree with the general applicability of expectant therapy in those cases classified as mild, where the patients are already in active labor and may be expected to deliver easily and with reasonable promptness. Finally, I agree that cesarean section must be employed in all cases of severe bleeding if delivery is not imminent, and when a "completely damaged uterus" is suspected. It is at this point that our attitudes differ, since we are inclined at the Evanston Hospital toward more liberal use of cesarean section for certain of the cases falling between these two extremes. During the last five years at the Evanston Hospital, we have treated 101 cases of premature separation of the placenta according to this general outline. These cases represent 1.1 per cent of 8,694 patients delivered during this five-year period. Forty-eight per cent of these cases of abruption were managed by cesarean section. There were no maternal deaths. There were 14 stillbirths and 6 neonatal deaths, giving a fetal salvage in this group of 80 per cent.

One other point is worthy of mention. The mere fact that a baby is dead in this circumstance suggests that, irrespective of the amount of external bleeding or lack of shock, the degree of separation must necessarily be extensive. Treatment by cesarean section is of course definitive, and if vaginal delivery is not immediately imminent, cesarean section should not be denied the patient merely because a living baby cannot be obtained. I do not mean to minimize the hazard of this extremely serious complication of pregnancy; but I do suggest that the liberal use of cesarean section imposes no added hazard to the mother, that its timely use will permit the survival of a significant number of mothers who might otherwise be lost, and that it will increase the fetal salvage. I think that Dr. Daro's figures do not speak against cesarean section but merely emphasize that, to attain its full usefulness, the procedure must be carried out early, and in anticipation of a catastrophe, rather than after the catastrophe has occurred.

DR. WALTER F. DILLON.—Abruptio placentate is in itself a dreaded complication of pregnancy, and its sequelae of fibrinogenemia and lower nephron nephrosis may kill the patient even though the uterus has been successfully emptied.

A leisurely reading of the abstracts of the six cases of maternal death shows some of the problems that are encountered in a County institution. Two patients died within thirty minutes of admission, another was admitted in convulsive seizure twenty hours after the first convulsion, another with a hemoglobin of 30 per cent which is not enough to cause a clinical cyanosis, and three of the 6 had no prenatal care. Prenatal care does not prevent abruptio placentae, but a patient who takes the trouble to seek it would have entered the hospital sooner and would have been in better physical condition. In contrast, at Lewis Maternity where there is closer contact between hospital and patient, there were 102 cases of abruptio placentae during the six and one-half year period ending in July, 1954, without any maternal death, but a comparable fetal mortality of 42 per cent, corrected to 37 per cent. In addition, 70 per cent of our cases were beyond 36 weeks.

Regardless of whether abruptio placentae is secondary to toxemia or senescent changes in the placenta, the sequence of events is the same, bleeding and separation. Fortunate indeed are the mother and infant who have the blood escape through the cervix since it warns the mother of impending danger and, second, does not act as a dissecting wedge to separate the placenta completely or extravasate into the muscle and cause toxic

changes in the liver or kidney. The incidence of these latter complications varies with the amount and duration of concealed hemorrhage. Even the mild cases with external bleeding will manifest albuminuria at some phase in the process.

The method of management is concerned with three phases: (1) treatment of the shock with blood replacement and fibrinogen if necessary; (2) delivery of the patient by: (a) The vaginal route if the cervix is effaced and open. This was accomplished in 93.4 per cent of our cases. Patients with abruptio placentate have fast labors, and simple rupture of the membranes may initiate the process. If not, intravenous Pitocin is the most useful adjunct. (b) Cesarean section (6.6 per cent) if heart tones are regular and the cervix is not ripe for immediate labor and delivery, or in the very rare case of concealed hemorrhage with a dead baby, and a thick, closed cervix. Cases with irregular fetal heart tones usually result in neonatal death because of the associated anoxia with resultant cerebral damage. (3) Observation and treatment of the patient following delivery to combat (a) hemorrhage which is on the basis of fibrinogen depletion if the blood does not clot. These patients require fibrinogen and bank blood or direct transfusion until the liver resumes its function of adequate fibrinogen production. Kellogg's method of examining drawn samples of blood to note clotting is the most practical method to determine the efficacy of treatment. Hysterectomy should be used only for bleeding from an atonic uterus, which is rare even in the so-called Couvelaire variety, as abruptio is associated with hypertonic uteri. (b) Lower nephron nephrosis may be overlooked unless the urinary output is measured following delivery. It is managed by supervision of fluid intake and electrolyte balance. It is usually corrected in 48 hours after delivery.

BLOOD PROTEIN-BOUND IODINE DETERMINATIONS AS A MEASURE OF THYROID FUNCTION IN NORMAL PREGNANCY AND THREATENED ABORTION*

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THE purpose of this study is to determine whether a relationship exists between the level of thyroid activity and reproductive performance in women. Before presenting the details of this study, it may be well to review some of the facts already available and current opinions on the subject. It is generally agreed that hyperplasia of the thyroid gland is physiologic during pregnancy, and it has been presumed that this reflects a normal increase in thyroid activity. The BMR (basal metabolic rate) normally shows a progressive increase beginning about the fourth month and rises to approximately plus 16 per cent at the end of pregnancy. The rate of oxidation is not controlled by the thyroid gland alone, however. Further, the rise in BMR in pregnancy is not accompanied by other recognized manifestations of hyperthyroidism. Serum cholesterol is reported to increase in pregnancy, a phenomenon that is regularly observed in hypothyroidism. Clinically, hyperthyroidism does not influence the normal course of pregnancy nor does it prevent conception. Habitual abortion and infertility have been attributed to varying degrees of thyroid deficiency.

In the last decade considerable attention has been focused upon the use of the PBI (serum protein-bound iodine concentration) as an objective method of evaluating thyroid function.[21, 22, 25, 26] Such a procedure is based on the well-established concept that the iodine-containing substance thyroxin either is the thyroid hormone or part of it.[27] Although the vast majority of the protein-bound material is thyroxin, traces of two other substances have been detected by chromatography. Gross and Pitt-Rivers[10, 11] have recently identified one of these to be 3:5:3′-l-triiodothyronine. They have also synthesized the compound and showed that it was about three times as potent as l-thyroxin in preventing goiter in rats treated with thiouracil. Because of this surprisingly high potency, Gross and Pitt-Rivers have suggested the possibility that l-triiodothyronine may be the form of the thyroid hormone that is active in the tissue.

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Increase in the concentration of serum PBI during the course of normal pregnancy has been well established by the work of Man and her associates.[12, 16] In nonpregnant euthyroid women the level of PBI varied from 4 to 8 gamma per cent. In pregnancy, the level increased to the values of 6.2 to 11.2 gamma per cent, rising sharply from normal in the early weeks of pregnancy and remaining at these levels until delivery, after which it rapidly returned to normal. The rise in the PBI could not be correlated with the rise in BMR. Danowski and co-workers[4] have demonstrated that the elevated PBI in serum was due to an increase in the "thyroxine" fraction. Further Man and her colleagues[16] presented data which suggested that the failure of the PBI to rise at the onset of pregnancy might lead to early abortion, and that this might be prevented by administration of thyroid substance. Their studies have been corroborated in part by the work of DeMowbray and Tickner,[6] and Russell.[23] The number of patients studied by these investigators was not large enough to warrant definite conclusions, however. Furthermore, most of their observations in normal pregnancy were of a sporadic nature rather than in the form of serial determinations of the PBI.

We felt that further investigation could be very fruitful in elucidating the relationship between pregnancy and thyroid function, and possibly in solving the problem of some "spontaneous" abortions of unknown etiology.

The present study was designed: (1) to determine serial values of PBI in a large number of normal pregnant patients, and (2) to see if there was any variation from normal values in patients receiving oral thyroid medication throughout their pregnancy, and (3) to determine PBI levels in patients with a diagnosis of threatened abortion with an eye to a possible prognostic significance.

Method

The PBI analytical procedure performed in our laboratory was the one devised by Sobel and Sapsin,[24] which was essentially a modification of Barker's method.[1, 2] Ten cubic milliliters of venous blood was drawn from patients in the fasting state, or after a morning meal consisting of fruit juice, black coffee, and toast. Precautions against iodine contamination were taken.

TABLE I. NORMAL PREGNANCY, 25 PATIENTS*

GESTATION (WEEKS)	NO. OF PATIENT DETERMINATIONS	PBI GAMMA % MEAN VALUE	STANDARD ERROR OF THE MEAN
6-8	18	7.52	0.283
12	23	7.01	0.334
16	25	7.44	0.280
20	21	6.99	0.305
24	23	7.41	0.209
28	24	7.23	0.286
32	20	7.54	0.246
36	13	7.58	0.361
Labor	16	7.73	0.225
First postpartum day	22	7.22	0.213
Third postpartum day	23	7.13	0.229
Fifth postpartum day	20	6.92	0.291
6 weeks post partum	25	6.58	0.140

*Complete data of the PBI determination may be obtained from the authors on request.

Material

1. Twenty-Five Normal Pregnant Patients (Table I).—Their ages ranged between 16 and 38 years; 16 were multiparas and 9 nulliparas. None of them showed any clinical evidence of thyroid dysfunction. The dietary habits of all these patients remained fairly constant during this study.

PBI determinations were carried out at monthly intervals beginning in the majority of patients at the sixth to eighth week of gestation. The determinations were repeated during labor, on the first, third, and fifth postpartum days, and at the check-up examination six weeks post partum. The majority of the determinations were done in triplicate and some even in quadruplicate, so the total number of analyses has approximated 900.

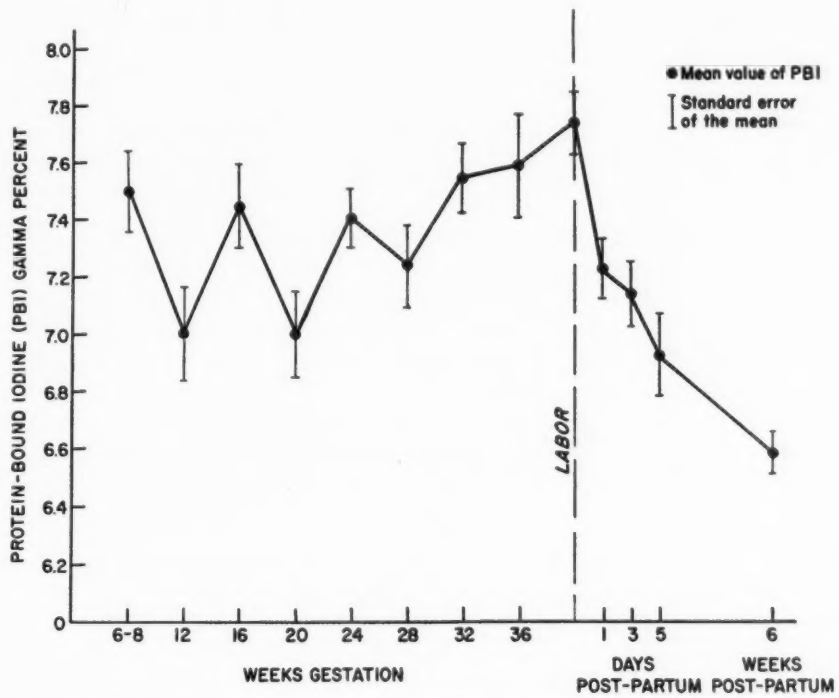

Fig. 1.—Graph illustrating blood PBI values during normal pregnancy, labor, and postpartum follow-up.

2. Four Pregnant Patients on Thyroid Medication.—The ages of these patients ranged between 21 and 29. They received oral thyroid substance daily for various reasons. One of them was a habitual aborter. Two others had had two and one previous spontaneous abortions, respectively. The fourth patient was given the thyroid on an empirical basis.

Serial PBI determinations were carried out in exactly the same manner as in the previous group of normal pregnant patients. Approximately 140 analyses were performed.

3. Thirty-Six Patients With a Diagnosis of Threatened Abortion.—The ages of these patients varied from 16 to 39 years; 28 were multiparas and 8 nulliparas. Serum PBI concentrations were measured in these patients immediately following their admission to the hospital. They were repeated ac-

TABLE II. PBI OF 26 PATIENTS WHO ABORTED

PATIENT	WEEKS*	PBI GAMMA %	TIME OF ABORTION p LAST PBI†	MEDICATION, THYROID, ETC.	REMARKS
1. F. G.	8	8.9			Missed abortion
	12	6.9			History of 1 previous stillbirth
	20	5.9	2½ weeks		
	p 1	6.5			
	p 6	6.3			
2. C. J.	8	7.8		Stilbestrol	Missed abortion
	12	7.5			
	16	6.2			
	20	7.9	1 week		
	p 1	8.5			
	p 6	5.7			
3. B. G.	10	7.1			
	11	6.5	3 days		
	p 1	5.4			
4. F. H.	9	6.7		Thyroid	Appendectomy at 6 weeks' gestation
	13	8.9		Stilbestrol	
	18	5.5	5 days	Progesterone	Missed abortion
	p 6	7.6			
5. O. M.	10	8.6, 8.2	3 days		
6. E. S.	17	8.0, 8.8	0 day		
7. B. L.	18	6.8	3 days		
8. A. T.	10	7.0	1 day		
9. D. H.	21	8.3	2½ weeks		
	p 1	9.5			
10. V. H.	20	6.4	5 days	Propylthiouracil	Pregnancy complicating hyperthyroidism
	p 1	8.0			
	p 4	7.7			
11. P. H.	8	5.4	1 week	Thyroid	
	p 1	6.1			
12. J. C.	22	8.7			
	24	11.2	4 weeks		Immature stillborn infant, 900 grams
	p 1	6.5			
13. V. P.	16	12, 11.8	−1 day		Hydatidiform mole
	p 1	7.7			
14. J. S.	17	8.6	?		
15. E. L.	7	8.5	2 days		
16. A. A.	17	7.7	1 day		
17. J. B.	8	6.7	1 week		
	p 1	6.1			
	p 4	5.2			
18. G. L.	14	6.4	?		
19. T. Y.	13	8.8	0 day		
20. M. B.	8	5.5	4 weeks		
21. B. M.	9	7.5	2 weeks	Progesterone	2 previous spontaneous abortions
22. S. B.	11	7.5	1 day		

TABLE II—CONT'D

PATIENT	WEEKS*	PBI GAMMA %	TIME OF ABORTION p LAST PBI†	MEDICATION, THYROID, ETC.	REMARKS
23. J. R.	19	7.0			
	20	8.0			
	21	7.0	0 day		
24. R. B.	17	6.5			Missed abortion
	18	5.0	1 week		3 previous spontaneous abortions
25. H. W.	16	8.6	5 days		3 previous spontaneous abortions
26. S. R.	14	7.5	1 week		

*If not otherwise marked indicates weeks after last menstrual period. "p" indicates weeks after delivery.

†A minus sign indicates that PBI was done after abortion, or that it was done on the day of abortion; ? that the precise interval is unknown.

cording to the change in the clinical status of the patient. The determinations were made in triplicate, the total number of tests performed having been approximately 200.

Results

1. Twenty-Five Normal Pregnant Patients.—In Table I and Fig. 1 are presented the values for PBI obtained serially in 25 apparently normal pregnant women. There does not appear to be any definite trend in the PBI levels, the values ranging between the euthyroid and hyperthyroid levels during pregnancy, labor, and the puerperium, and returning to euthyroid levels at six weeks post partum. These results agree closely with the findings of others and support the conclusion that normal pregnancy is usually associated with a rise in the serum PBI. The highest and lowest values observed were 10.5 and 3.0 gamma per cent, respectively. No discernible clinical signs of thyroid dysfunction were evident in these subjects, or in those with lesser elevations in PBI. The results of our serial analyses indicate that the rise is not necessarily stable. At times slight but probably definite fluctuations in serum PBI levels were observed, while in others previous values were reduplicated.

2. Four Pregnant Patients on Thyroid Medication.—The administration of thyroid to 4 patients throughout the pregnancy did not cause any significant increase in the PBI levels. In fact, the values fell within the same range as observed in the other normal pregnant patients.

3. Thirty-Six Patients With a Diagnosis of Threatened Abortion.—The results to date may be summarized as follows:

A. Twenty-six patients have aborted. The PBI levels in all of these patients were in the euthyroid to hyperthyroid range (Table II). One of them (V. P.) with a diagnosis of hydatidiform mole had abnormally high values of 12 and 11.8 gamma per cent. These returned to normal values one week following the passage of the mole. One patient (J. C.) went into premature labor at 28 weeks and delivered a stillborn fetus. At 24 weeks' gestation she showed a high level of 11.2 gamma per cent. Post partum, her PBI returned to normal levels.

B. Five patients carried their pregnancies to term and delivered viable normal infants. Their PBI levels were within the normal range at the time they were threatening to abort.

C. The remaining 5 patients are continuing their pregnancies satisfactorily. Their PBI levels have ranged between euthyroid and hyperthyroid values at a time when they presented clinical evidence of threatened abortion.

Comment

From the present studies and the experience of other investigators evidence has been obtained which strongly suggests the reality of the rise in circulating protein-bound iodine in normal pregnancy. The results of our serial analyses indicate that there is no particular period during gestation at which the rise in PBI to upper euthyroid or hyperthyroid levels occurs; it might be at six weeks or at three months. Further, the rise is not necessarily stable and considerable individual variation is noted in each patient. Following delivery there is a very gradual decline in the PBI levels during the first five postpartum days, but they return to normal nonpregnancy values within six weeks (Table I). No other statistically significant findings were observed.[19]

Our data on 4 pregnant patients, who received thyroid throughout pregnancy and post partum for two to three months, indicate that in no instance did the medication increase PBI above the normal range for pregnancy.

While the exact mechanisms involved in the increase of serum PBI during pregnancy remain unknown, certain factors which possibly operate in inducing such a change are worthy of speculation. It is possible, as Man[16] has suggested, that the pregnant woman tolerates a greater concentration of hormone in her serum or that the increment is not composed of thyroid hormone. Danowski[4] has shown that the rise in the PBI in uncomplicated pregnancy is associated with an increase in the thyroxin fraction of the PBI. No data are as yet available in human pregnancy to show that the concentration of circulating thyroxin and PBI can be affected by the rates at which these compounds are synthesized, released from their sites of origin, metabolized, and excreted. In a recent study Danowski[5] has attempted to show that elevated PBI levels in pregnancy represent a "steady state." Exogenous administration of thyroxin to 10 normal pregnant patients was not associated with any discernible abnormality in the absorption, protein-binding capacity, or distribution of thyroxin. Nor was there any change in its subsequent dissociation, degradation, or excretion. It is possible, however, that radioactive tracer studies in human pregnancy will further elucidate some of these problems.

In recent years renewed interest in the thyroid-adrenal relationship has been stimulated by experimental and clinical observations[8, 13, 17, 29] which indicate that alterations in the availability of certain adrenocortical steroids may induce pronounced changes in the metabolism of iodine. While these changes have been variously ascribed to effects of cortical steroids on the pituitary gland,[13] the thyroid, and the kidney,[20, 28] resolution of the precise modes of their action is not yet complete. Gemzell[9] has shown that the blood levels of 17-hydroxycorticosteroids in normal pregnancy are much higher than those of normal nonpregnant women and that these levels rise progressively until the end of gestation. It is possible that these steroids, like cortisone,

might decrease the rate of peripheral utilization of thyroid hormone, thereby resulting in an augmentation of the PBI. This hypothesis would be in keeping with the animal experimental work of Bondy and Hagewood.[3] Other observers,[7, 13, 15, 18] however, have shown that cortisone does not alter or directly affect the peripheral utilization or degradation of thyroid hormone in man. Whether this increase in PBI in human pregnancy results from an increase in the glandular production of the hormone, the rate of turnover of the glandular hormone pool, or both, and whether it is mediated by an action of the adrenal cortical steroids on the pituitary gland or directly on the thyroid remains to be elucidated.

In Table II are recorded the data of 26 patients who aborted. In only 5 of these patients was the PBI less than 6 gamma per cent, a figure arbitrarily chosen by Man[16] as representing the optimal lower level prior to 16 weeks' gestation for successful continuation of pregnancy. Our data, in contrast with those of Man, tend to suggest that a low PBI is not associated with abortion, nor is a high PBI any guarantee against abortion. Such an inference, however, must be drawn with reservations, as our figures do not permit any definite conclusions, chiefly because single observations are available in the majority of our patients.

From our study of a limited number of patients with a diagnosis of threatened abortion, one wonders if such patients should be given thyroid routinely on an empirical basis. While such a practice is followed by the majority of physicians, it would take a much larger control study to prove the value of thyroid medication. Even then, in so far as the thyroid gland is only one of the glands necessary for successful termination of pregnancy, the problem would remain unsettled for some time to come.

Summary and Conclusions

1. PBI determinations were performed serially in a group of (a) 25 apparently normal pregnant women and (b) 4 pregnant women who were maintained on thyroid medication throughout gestation. Observations were recorded at regular monthly intervals during pregnancy, and also during labor, and on the first, third, and fifth days post partum, and six weeks later. Although there was no uniformity in the height, time of appearance, or duration of the elevation, these studies confirmed the fact that elevations do occur in the PBI levels during pregnancy. The values declined gradually in the puerperium and returned to nonpregnancy levels by six weeks post partum. The administration of thyroid hormone in 4 pregnant patients did not appear to influence the PBI levels at all.

2. PBI levels were also determined in 36 patients who showed clinical evidence of threatened abortion. Among the 26 patients who aborted and the 5 patients who continued successfully to deliver viable infants at term, the values ranged between normal and hyperthyroid levels. The 5 patients who are continuing with their pregnancies satisfactorily also had levels in the normal pregnant range.

3. The significance of these findings has been discussed in the light of recent literature.

Grateful acknowledgment is made to Dr. Morris Rochenmacher, Chief of Clinical Laboratories, Los Angeles County Harbor General Hospital, for his cooperation and help in the supervision of the PBI Laboratory. We also wish to thank Dr. Wilfrid J. Dixon, Professor of Biostatistics, U.C.L.A. School of Medicine, for his assistance in the statistical evaluation of the data presented.

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THE PROBLEM OF SPONTANEOUS ABORTION*

II. Changes in the Placental Villi

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IN UNDERPOPULATED countries the incidence of spontaneous abortion, with its effect on the live-birth rate, has a politicoeconomic significance which outweighs in importance all other diseases whose lethality engages the attention of medicine. It is generally accepted that spontaneous abortions result in 10 per cent of all pregnancies and it takes but little reflection to realize that a reasonable reduction in this figure would be of immense benefit to any community not threatened by Malthusian postulates.

There is very little agreement on the cause or causes of spontaneous abortion. Paine[1] believed that there may be two: either improper implantation of the ovum or expulsion of a dead, defective ovum. Huntingdon[2] considered a defective germ plasm the cause; Montgomery,[3] acute placental inflammation secondary to intrauterine infection. Javert and Finn[4] inclined to multiple factors with decidual hemorrhage high on the list. Hertig and Edmonds[5] described a blighted ovum with hydatidiform changes in the villi. McNeil and Fullmer[6] proposed maternal-fetal ABO incompatibility, an association previously suggested by Waterhouse and Hogben,[7] while Hall[8] considered that insufficient attention had been given to the villous basement membrane. It was decided to investigate the problem from the clinical, biochemical, endocrinological, psychiatric, and pathological viewpoints. This report deals with the pathological findings only.

Material and Methods

The placentas and, whenever possible, the fetus from 47 spontaneous abortions occurring between the eighth and sixteenth week of pregnancy were examined, as well as the placentas in 9 cases of threatened abortion which came to term or near term.

The controls consisted of placentas from 22 cases covering one to nine months' gestation, all with a normal obstetrical history but in the younger age group with an abnormal medical background. The specimens from the latter were obtained when surgical intervention was demanded by the non-obstetrical illness of the mother. The placents from 5 cases of toxemia were added to widen the basis of comparison.

From each case, three samples of placental tissue were taken at random as well as further sections from any area in the organ showing gross pathological changes. The paraffin blocks obtained were cut at 10 microns, a thickness found by trial to give the best results. The sections were stained with hematoxylin and eosin; Van Gieson's method for collagen, Hotchkiss' periodic

*The investigation has been supported by a Federal Health Grant throughout.

acid-Schiff technique; the standard toluidine blue method for metachromasia; Feulgen's reaction (Feulgen and Rossenbeck modified by de Tomasi); Perls' method for ferric iron, the von Kassa and alizarin red methods for calcium, and the eosin-Gram-Weigert method for fibrinoid.

Results

The placental villi in 38 of the abortions showed histological changes which will be described in detail; 9 were normal when compared with the controls.

There were 3 abnormal fetuses, an anencephalic, a cyclops, and a blighted ovum. The villi of the first two showed the lesions related to abortion, while the third showed the typical senile villi of a placenta at full term. The placental villi of those women with threatened abortion who ultimately went to term and were delivered of a living child, with 2 exceptions, showed no detectable abnormalities. The two exceptions ended in premature delivery and scattered villi showed the same alterations seen in spontaneous abortion.

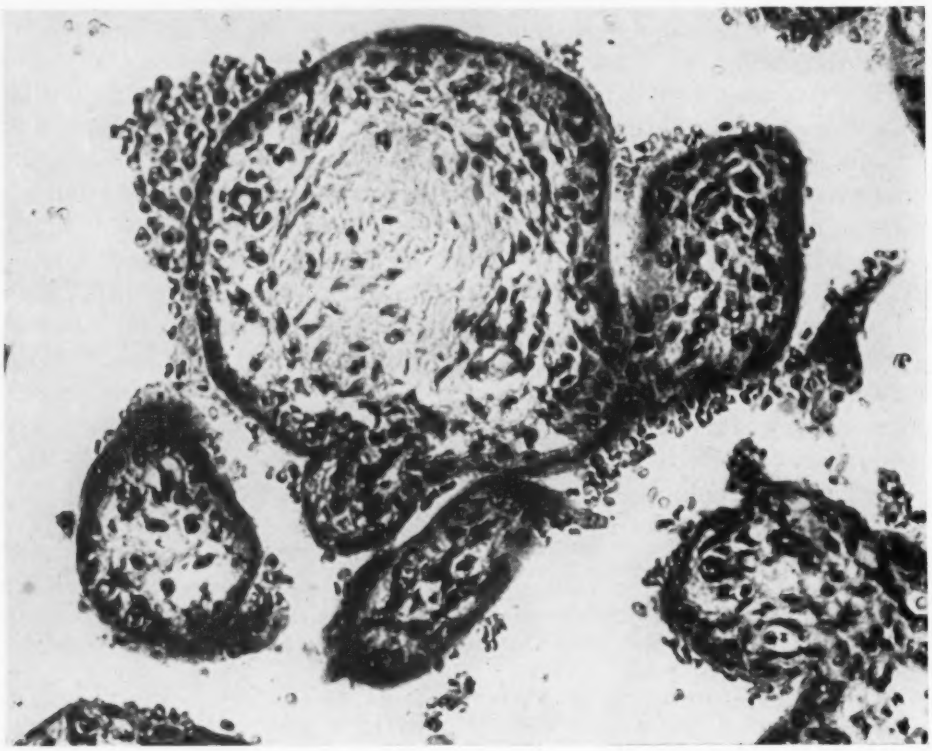


Fig. 1.—Villus demonstrating fibrinoid necrosis. (Hematoxylin and eosin, ×750; reduced ½.)

The Lesions in the Villi in Spontaneous Abortion

Hematoxylin and Eosin and Van Gieson's Stain.—The earliest changes seen with the hematoxylin-eosin stain consists of a circular or ovoid plaque of fibrinoid necrosis lying in the center, or somewhat off center in the villus. At the periphery of the plaque the stromal nuclei have become spindle shaped and lie concentrically in thickened bundles of stromal substance. This area fades into a rim of the fine areolar strands and ovoid nuclei of a normal villus.

The epithelium appears normal although in an occasional villus it may be surrounded by a thin layer of fibrin. The intervillous spaces contain no substances of pathological importance. The whole of the villus matrix is eventually engulfed in fibrinoid necrosis (Fig. 1), leaving the nuclear remnants as dark deposits embedded like currants in a cake. The epithelium has thinned, the nuclei are ovoid and pyknotic, lying like a thin chain around the affected villus.

The intervillous space is not remarkable. The final stage is shown by complete hyalinization of the villus outlined by a thin rim of epithelial nuclear remains (Fig. 2). About one half of the placentas obtained from abortion showed these lesions. The distribution of collagen in the placental villus was observed in the controls and cases of abortion.

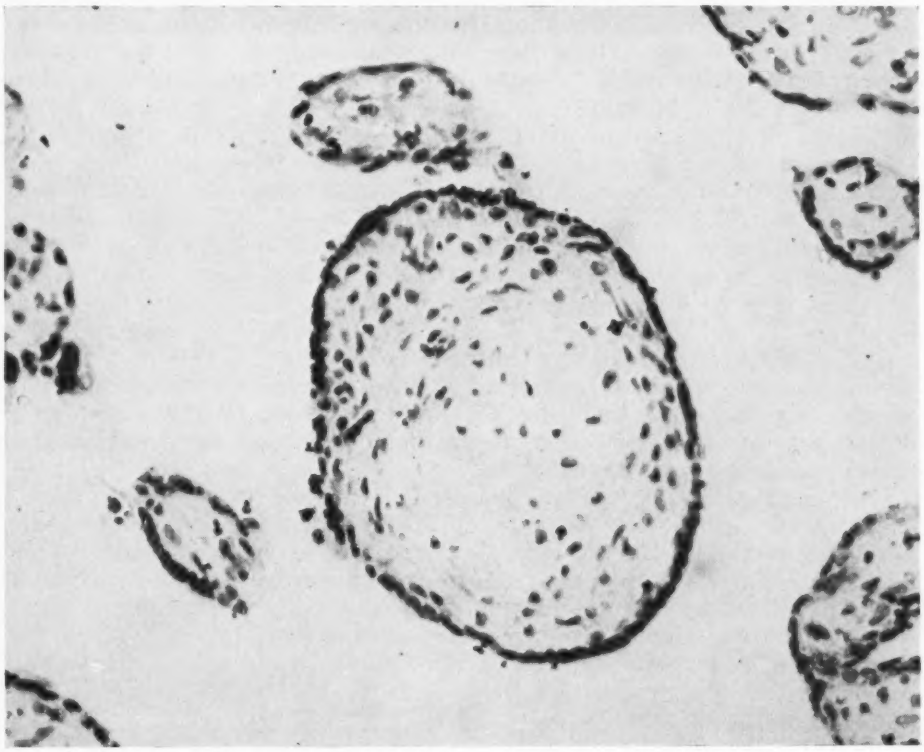


Fig. 2.—Villus showing complete hyalinization. Note the epithelial atrophy. (Hematoxylin and eosin. ×750; reduced ½.)

In a normal pregnancy of approximately one month's duration the stroma of the villus is free of collagen (Fig. 3). An occasional stalk shows a flare of very fine collagen fibrils spreading along the areolar strands. At seven months the villi are still free of collagen, but surrounding the vessels of the larger stalks is a fibrillary collagenous condensation arranged in a circular manner. At term the collagen in the villi is restricted to a moderate perivascular condensation and in the stalks the collagen perivascular layer has become much denser.

In the placentas of abortion, collagen when it appears is laid down in coarse fibers usually in parallel rows in the affected part of the villus. These

patches bear no relation to the blood vessels and may appear anywhere in the villus areolar network. It is this erratic distribution of collagen which is characteristic of villus damage demonstrated by this stain (Fig. 4).

As the lesions progress, the collagen fibers become thicker and more confluent until eventually a plaque is formed which breaks down to form the areas of fibrinoid necrosis in which lie scattered red remnants of collagenous material. The precursor to the stage of fibrinoid necrosis and hyalinization was not appreciated until Van Gieson's stain was used. The thickening of the areolar fibrils to form massive collagenous bands appears to antedate the stage of fibrinoid necrosis.

In 6 of the cases of abortion, lesions which might have been missed by routine hematoxylin and eosin sections were picked up by changes shown with the Van Gieson stain.

Eosin-Gram-Weigert Stain.—Although the oval or circular areas of necrosis seen in the villi with the hematoxylin and eosin staining have been termed fibrinoid, it is obvious that tinctorial evidence must be presented as proof before they can in reality be classed as such. With the eosin-Gram-Weigert stain fibrinoid takes on a deep purple-blue color. Fig. 5 shows a necrotic area lying within a villus stained by this method. It is strongly positive and there seems to be little doubt that the term fibrinoid necrosis is justified in describing the lesions demonstrated with previous staining methods.

The distribution of affected villi in a placenta is variable, there being loci of normal tissue adjacent to loci of abnormal and comparatively few or many areas may be involved, varying from case to case. In any given placenta where the villi show this stigma, however, the stage of development between fibrinoid necrosis and hyalinization is fairly uniform, suggesting that when the damage originally occurred all the affected villi were injured at approximately the same time and the point at which they are seen in the evolution between necrosis and hyalinization depends on the duration of the pregnancy after the injury to the villi.

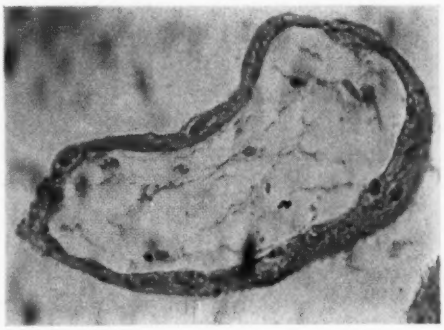
There is a striking difference between the histological picture presented by the common white infarcts of the placenta and the lesions that occur in spontaneous abortion. In the first all the villi in a circumscribed area have been attacked in contrast to the patchy distribution in abortion; further, the intervillous spaces in white infarction are packed with fibrin, in spontaneous abortion the intervillous spaces are clear; third, the villous epithelium is invariably completely destroyed in infarction while in abortion it persists in a recognizable form to the end.

Periodic Acid-Schiff Technique.—In the normal, the epithelium lies on the rim of a thickened circular stromal band staining lilac. The nuclei tend to project into the intervillous space. The villus stroma stains a faint lilac; both epithelial and stromal nuclei take up the celestin blue strongly. Around some of the villus knots are blobs of an exudate purplish red, possibly a mucoprotein. However, only a few scattered knots in any field show this surround of a strongly positive periodic acid-Schiff reaction.

In the placentas obtained from abortion, however, the picture is vastly different. In the stroma of the villi, the nuclei are surrounded by what appears to be a reddish-purple cytoplasm out of which small strands of the same material protrude.

The epithelium is embedded in an exudate of a reddish-staining material shutting off the villus epithelium from direct contact with the intervillous space. The stromal nuclei take up celestin blue poorly, suggesting degenerative changes. The epithelial nuclei, on the other hand, stain fairly well.

Fig. 3.



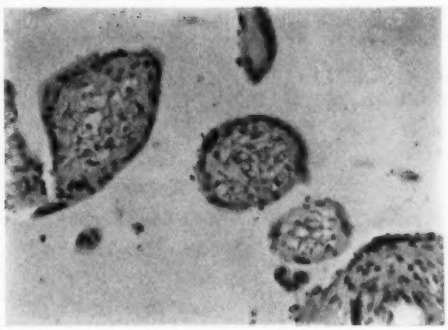
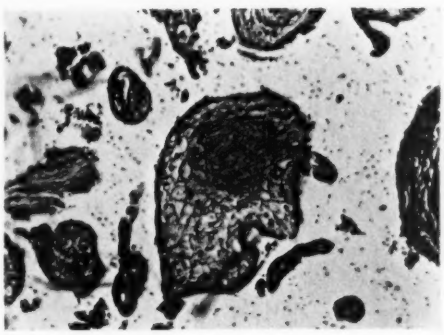


Fig. 4.

Fig. 5.



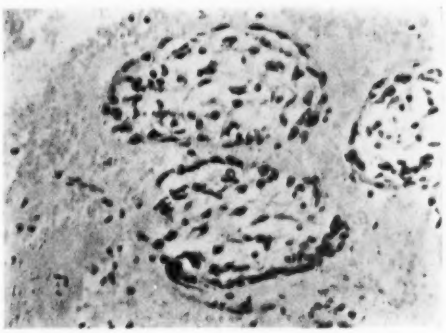
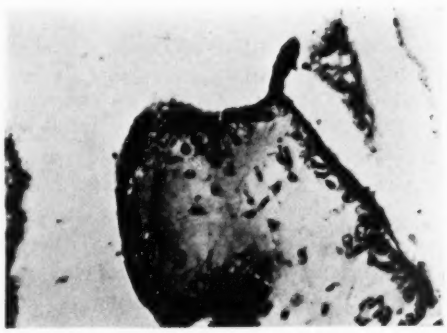


Fig. 6.

Fig. 7.



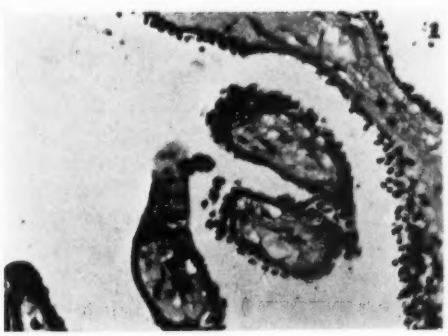


Fig. 8.

Fig. 3.—Villus from a normal placenta at approximately a month's pregnancy. (Van Gieson stain. ×750; reduced approximately ½.)

Fig. 4.—Villi showing the collagenous changes in spontaneous abortion. (Van Gieson stain. ×375; reduced approximately ½.)

Fig. 5.—Villus containing necrotic focus. (Eosin-Gram-Weigert stain. ×500; reduced approximately ½.)

Fig. 6.—Villi from normal placenta at about the third month. (Toluidine blue stain. ×500; reduced approximately ½.)

Fig. 7.—Villus from a case of spontaneous abortion showing marked subepithelial metachromasia. (Toluidine blue stain. ×750; reduced approximately ½.)

Fig. 8.—Villi from a case of spontaneous abortion showing metachromasia of the stromal fibers. (Toluidine blue stain. ×500; reduced approximately ½.)

In the villi of those cases in which lesions have gone on to fibrinoid necrosis or hyalinization the specifically affected areas vary greatly in their response to PAS.

In contrast to the picture presented by the hematoxylin and eosin stain where scattered villi show pathological changes, the reverse is true with periodic acid-Schiff stain, in that nearly all the villi show alterations from the normal, although the intensity may vary from case to case, indicating that in abortion the functional derangement of the villi is greater than ordinary routine staining would indicate.

Seven cases of abortion showing an apparently normal villus pattern to the hematoxylin and eosin and Van Gieson staining were strongly positive with periodic acid-Schiff technique. All the cases that were hematoxylin and eosin and Van Gieson positive showed periodic acid-Schiff changes of varying intensity.

Toluidine Blue Reaction for Metachromasia.—In the normal villus there are no metachromatic changes to be seen in the ground substance or areolar network (Fig. 6).

In 6 cases of abortion where examination by hematoxylin and eosin and Van Gieson were negative and the periodic acid-Schiff stain equivocal, metachromasia was very evident. This appears in one of three forms: In the first, the ground substance and areolar fibrils lying next to the epithelial border show as a deep red, the intensity of the color fading as it spreads centripetally (Fig. 7). In the other, the ground substance and the areolar fibrils in the whole central area of the villus show a fainter red, while the epithelial border is clear. Third, the lesions advance to a thickening and proliferation of the stromal fibers, which remain markedly metachromatic positive, while the intervening ground substance is negative (Fig. 8).

When fibrinoid necrosis and hyalinization have occurred, the affected areas show intense metachromasia.

Feulgen Reaction for Desoxyribonucleic Acid (DNA).—The Feulgen reaction was used to indicate the presence of desoxyribonucleic acid in the nuclei of the villus cells. In the normal placenta of a one months' pregnancy, the reaction is negative. At about the fifteenth to the sixteenth week, the nuclei in the epithelium are moderately positive for DNA. As the pregnancy progresses, the concentration of DNA rises, greatest in the syncytial knots, less in the epithelial nuclei, and least of all in the stromal. Abortion does not alter this picture.

In this series, one case of abortion occurring in the third month of pregnancy showed a blighted ovum. The DNA reaction of the epithelium was intense, and paralleled that seen in the placenta at term, indicating that in this particular case the placenta had gone from birth to senility in a matter of weeks instead of months.

The concentration of DNA in the nuclei is useful in checking the physiological age of the pregnancy in relation to the chronological. In one case, the chronological age was given as 23 weeks, but the DNA concentration put it near 15. In 3 others, the pregnancy was older than the period suggested by the patient's dates, varying from four to six weeks.

Calcium and Iron.—The findings in this series for both calcium and iron were similar to those reported by other investigators. In 6 of the cases of abortion gross amounts of iron were present. In these it lay in massive subepithelial deposits and on the areolar network of the villus. It was, on the whole, confined to the villus stroma and did not appear to be related to blood vessels.

Comment

Whether the lesions described are due to the death of the fetus or precede and may therefore be the primary cause in many cases of spontaneous abortion must for the present be left undecided. It is a useful pointer, in distinguishing between the post hoc and propter hoc relationships, that in 2 cases of premature delivery live babies were obtained, the placentas of which showed scattered villus hyalinization, identical with that seen in many of the cases of spontaneous abortion. Further work on this part of the problem must be done before the probability can be known.

It is unfortunate that the histological changes found in any given case of abortion tend to follow an all-or-none pattern. In one case, the affected villi show metachromasia and little else, in another fibrinoid necrosis and no hyalinization, while in a third, hyalinization with but focal PAS changes. If reasonable overlapping occurred, it would make simple an attempt to link metachromasia and hyalinization as different stages in an irreversible progression.

There is one thread, however, running throughout which suggests that the lesions seen with various staining methods are intimately related.

Gamma metachromasia is usually indicative of acid mucopolysaccharide and its presence in the ground substance and areolar fibrils in the villi of abortion and not in the normal indicate that its appearance is a reflection of a fundamental alteration in the chemical properties of the villus mucus.

It has been shown that the plethora of fibrils found in the PAS material giving a positive reaction also react metachromatically with toluidine blue, suggesting that acid mucopolysaccharide has entered their formation. At the same time the ground substance no longer reacts with toluidine blue which, because of the fibrillary proliferation, must be reduced in quantity.

Pearse,[9] on very good grounds, has suggested that collagen is formed by the cementing together of reticulin fibrils by a proteinlike substance containing variable amounts of polysaccharide. On the evidence now available, the following hypothesis is put forward to explain the sequence of events leading up to the formation of collagen in the villi in spontaneous abortion. Some unknown irritant or irritants pass through the villus epithelium to react with neutral mucopolysaccharide to form the acid variety. The molecules of acid mucopolysaccharide attach themselves to the surface of the fibrils of the areolar network and at the same time the stromal nuclei whose function is to regulate the internal milieu of the villus create further reticulin fibrils in response to the acid mucopolysaccharide stimulus. That the stromal nuclei are implicated seems the only credible explanation for the periodic acid-Schiff positive exudate that surrounds them at this period in the progress of the lesion. The reticulin fibrils with their attached mucopolysaccharide become bound together to form the bands of collagen. It may be thought that this process continues until most of the acid mucopolysaccharide has been removed. This latter point is suggested by the markedly gamma-metachromatic fibers seen in the presence of nonmetachromatic ground substance. The broad bands

of collagen thus formed eventually break down to present the picture of fibrinoid necrosis which ends in hyalinization. That this breaking-down process is accompanied by the release of acid mucopolysaccharide is suggested by the fact that these lesions are associated with marked gamma metachromasia.

If this hypothesis has any validity, then it follows that steps from ground substance metachromasia to the hyalinization of the villi are but varying aspects in the orderly progression of the lesion from its near genesis to its end. The point at which abortion will occur along this march depends on the functional capacity of the damaged villi in relation to the demands of the fetus and it is presumably for this reason that the developmental pattern of the lesion is much the same in most of the villi examined in an affected placenta.

Histologically, the presence of collagen, fibrinoid necrosis, and hyalinization in intravillous lesions suggests that it be classed among the collagenoses (connective tissue diseases)—a heterogeneous group with, at present, apparently diverse pathogenesis. There is considerable argument as to whether or not ground substance hypersensitivity plays an essential role in the production of the condition, but it is a possible factor which must be borne in mind when the ultimate cause of these lesions is considered, particularly in the light of the growing awareness of maternal-fetal incompatibilities.

That not all cases of spontaneous abortion are related to the villus changes described is shown in this series. In 9 cases the placentas were normal and in the placentas of 9 threatened abortions which went to term or near term, only 2 showed scattered affected villi, the others being within normal limits. It must be considered that another cause or causes must be sought for the explanation of this latter type.

Summary

The placentas in 47 cases of spontaneous abortion have been examined histochemically. In 38, lesions showing the stigmas of collagenosis were found. Nine were apparently normal.

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SICKLE-CELL ANEMIA IN PREGNANCY

A Review of the Literature With Additional Case Histories

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IN THE past ten years the number of reported cases of sickle-cell anemia in pregnancy has increased to such an extent that this condition is no longer a rarity. To date 129 cases of sickle-cell disease in pregnant women have been reported.[1-46] The purpose of this paper is to report 9 additional cases of sickle-cell anemia in pregnancy observed at Harlem Hospital with a complete review of the literature and a summary of current concepts of diagnosis and treatment.

Sickle-cell anemia or disease is a hereditary, chronic disease of Negroes with protean manifestations involving virtually every system of the body. It is characterized by marked anemia, evidence of red blood cell destruction (jaundice and elevated icterus index), and sickle-shaped red blood cells.[47] It has latent and acute phases, the acute phase being called the "crisis." Sickle-cell disease is to be differentiated from sicklemia or the sickle-cell trait, in which there is no anemia or red blood cell destruction and which has no clinical significance.

Sickle-cell disease was first described by Herrick[48] in 1910. In 1924 Sydenstricker[49] surveyed the literature and reported additional cases. Up to that time he was able to find 80 cases; 90 per cent had only the sickle-cell trait, and 10 per cent had the clinical disease. In this report Sydenstricker mentioned 2 women with the sickle-cell trait who had apparently normal deliveries. It was not until 1931, however, that Yater and Mollari[1] reported the first case of pregnancy in a woman with sickle-cell disease.

There are wide variations in the reported incidence of the sickle-cell trait among Negroes. In the United States the incidence ranges between 7 and 14 per cent, whereas in Africa the frequency is as high as 20 per cent.[50-52] The incidence of sickle-cell disease varies from 0.2 to 1 per cent, with the ratio of sickle-cell disease to sickle-cell trait being between 1:9 and 1:71.[49-51] Originally, this disease was supposedly found only among Negroes. There have been a number of reports, however, of both the trait and the disease in white people.[5, 53-56] The individuals involved were usually from one of the Mediterranean countries or Latin America, and the possibility of Negro ancestry cannot be excluded in some of these cases.[57]

The sickle-cell trait generally does not appear until the fourth or fifth month of life.[45] Usually the disease first manifests itself in childhood, although

rare cases in infancy and one in a newborn infant have been reported.[58] The incidence decreases after adolescence, and most patients die before reaching their fourth decade or shortly thereafter.

It is believed that sicklemia is transmitted by a single dominant gene according to Mendelian laws. Why the disease develops in some and not in others is not known. Neal[59] explains this by offering an alternate hypothesis. He postulates that sicklemia occurs in a heterozygous individual, while sickle-cell disease results from genes in a homozygous individual.

General Description of Sickle-Cell Disease

Etiology and Pathogenesis.—It is beyond the scope of this paper to do more than mention briefly the various theories of the cause of sickling and of crises. Sickling has been attributed to reduced oxygen tension in the blood, variation in intracellular potassium concentration, alterations in the pH and temperature of the blood, and defects in sickle-cell hemoglobin.[39, 60] Crises have been attributed to numerous causes, some of which are a neurogenic or allergic factor, vascular spasm, a hemolytic process, bone marrow aplasia, thromboses with infarction, and obstruction of the blood vessels to the central nervous system.[61]

Clinical Manifestations.—Sturgis[62] stated that the crises usually fall into one of the following patterns: (1) febrile, (2) arthritic, (3) cardiovascular, (4) neurological, or (5) pneumonic. None of these syndromes has any pathognomonic symptoms or signs. Clinical differentiation from the more common diseases—influenza, rheumatoid arthritis, rheumatic fever and heart disease, cardiac failure, pneumonia—is often extremely difficult, if not impossible. Besides these fairly clear-cut patterns, the presenting complaints may include such diverse symptoms as epistaxis, hematuria, psychiatric disturbances, gall bladder disease, priapism, abdominal pains simulating "surgical abdomen," and generalized muscular and bone pain. During the crisis, fever, severe anemia, and some degree of icterus are present. Hepatosplenomegaly is also a fairly constant finding.

Diagnosis.—Sickle-cell disease has been termed the "little imitator"[47] and the "great masquerader,"[63] because of its ability to involve virtually any organ of the body and to simulate almost any disease. Sickle-cell disease should be considered in every Negro patient who gives a history of leg ulcers or scars, rheumatic fever or heart murmurs, jaundice, recurrent generalized muscular or abdominal pain, anemia, weakness, fatigue, dyspnea, tachycardia, recurrent upper respiratory infections, fever of undetermined origin, or epistaxis. Any bizarre symptomatology should suggest sickle-cell disease.

Absolute diagnosis depends on the demonstration of sickle cells in association with the clinical manifestations. Some workers use an ordinary blood smear with a cover slip rimmed with vaseline. By this method sickling will appear in 2 to 24 hours. Incubating the slide or placing it in a carbon dioxide chamber may hasten the process. Others recommend mixing sodium hydrosulfite with the blood; if sickling is present, it will appear in 3 to 30 minutes.

Experience at Harlem Hospital With Sickle-Cell Disease in Pregnancy

Nine cases of sickle-cell disease in pregnancy have been diagnosed at Harlem Hospital from January, 1945, to March, 1955. During this period there were approximately 51,000 pregnancies, including abortions and ectopic pregnancies, on the Obstetric and Gynecologic Services. About 97 per cent of our patients are Negroes.

TABLE I. SICKLE-CELL DISEASE IN PREGNANT WOMEN

PATIENT	AGE	TOTAL PREGNANCIES	PREGNANCIES AT HARLEM HOSPITAL	ABORTIONS	DELIVERY	VIABLE BIRTH	LIVE BABIES
E. M.	22	1	1	0	Spontaneous	1	1
I. T.	31	2	1	0	Both normal	2	2
L. B.	18	1	1	0	Spontaneous	1	0
D. F.	26	3	2	2	Low forceps	1	1
O. G.	19	1	1	0	Spontaneous	1	0
A. J.	25	2	1	1	——	1	1
R. A.	33	5	4	1	——	4	2
L. D.	23	1	1	0	——	1	1
F. F.	26	2	2	0	——	2	2
Total		18	14	4		14	10

There were 18 pregnancies in nine mothers with sickle-cell disease, with one maternal death. Of 14 viable pregnancies there were 10 surviving babies, a total fetal loss of 8 infants. A complete summary of the nine cases is given in Table I.

Sickle-Cell Disease and Pregnancy in 138 Total Cases

There is apparently a marked decrease in the frequency of sickle-cell disease in pregnant women, even when compared with the lowest incidence (0.2 per cent) of the disease in the general Negro population:

	CASES PER 10,000 POPULATION
Nonpregnant Negroes	20 (0.2%)
Pregnant Negro women	
Beacham and Beacham[31]	6
Anderson and Busby[22]	7.7
Harlem Hospital	2.7

All cases recorded in the literature and their available obstetric histories are summarized in Table II.

AT HARLEM HOSPITAL, JANUARY, 1945, TO MARCH, 1955

DEAD VIABLE BABIES	TOTAL FETAL LOSS	MATERNAL COMPLICATIONS	TIME OF DIAGNOSIS	COMMENT
0	0	None	Seventh month of gestation	Sickle-cell disease diagnosed because of severe anemia. No further pregnancies after 9 years; then cornual resections for bilateral pyosalpinx
0	0	None	Between pregnancies	——
1	1	Sudden death 5 hours post partum	Undiagnosed ante mortem	Anemia noted antenatally, treated with iron. Premature stillborn infant
0	2	Pneumonia twice, pyelonephritis	After second abortion	One year after diagnosis, live baby delivered
1	1	None	Antepartum	Previously diagnosed as rheumatic heart disease and osteomyelitis; hip lesion resembling aseptic necrosis of head of femur also present. Stillborn infant
0	1	None	First gestation	——
2	3	None	Second gestation	Previously diagnosed as rheumatic heart disease; questionable aseptic necrosis of head of femur present
0	0	None	3 days post partum	Sickle-cell disease detected when crisis developed. Previous diagnosis rheumatic fever
0	0	Transient postpartum cerebral disturbance resembling subarachnoid hemorrhage but spinal fluid clear	Childhood	Also diagnosed as rheumatic fever; cerebral embolism with hemiplegia at age 12
4	8			

TABLE II. SUMMARY OF 138 RECORDED CASES OF SICKLE-CELL DISEASE IN PREGNANCY

	PREVIOUSLY RECORDED		HARLEM HOSPITAL		TOTAL	
	NO.	%	NO.	%	NO.	%
Mothers	129		9		138	
Maternal deaths	29	22.5	1	11.1	30	21.7
Total pregnancies	268*		18		286	
Spontaneous abortions	51	19.3	4	22.2	55	19.5
Viable pregnancies	200†	75.2	14	77.8	214	75.3
Surviving babies	152‡		10		162	
Dead viable babies	43		4		47	
Total fetal loss	109	41.8	8		117	41.9

*In 2 instances the outcome of the pregnancy is not known; 3 patients had therapeutic abortions, one a salpingectomy (ectopic?).

†This figure does not include 11 patients who died undelivered.

‡In 5 cases the fetuses were viable, but their fate was not mentioned.

Maternal Age.—Since individuals afflicted with sickle-cell disease do not have a life expectancy past the fourth decade, one does not expect to find many

older patients in this series. Previously, 12 women of over 30 years of age have been reported.[12, 13, 17, 21, 26, 29, 31, 36, 37, 44] The two additional cases in our series make a total of 10.2 per cent. The oldest patient recorded was 35 years of age.[12]

Maternal Complications.—The most frequent complications are infections—urinary, respiratory, and puerperal—followed by toxemias of pregnancy (Table III). As will be shown in the discussion of maternal mortality, however, these complications do not play critical roles in the present-day management of these cases.

TABLE III. SUMMARY OF MATERNAL COMPLICATIONS IN 138 CASES

COMPLICATION	NUMBER IN DUCKETT AND DAVIS'[44] COMPILATION	OTHERS	HARLEM HOSPITAL	TOTAL
Urinary tract infection	25	2	1	28
Toxemia	23	5	5	28
Acute respiratory infection	18	5	2	25
Puerperal morbidity	21	1	0	22
Thrombophlebitis	5	0	0	5
Cerebral accidents	4	0	1	5
Tuberculosis	3	0	0	3
Cardiac failure	2	0	0	2
Interstitial pulmonary edema	0	1	0	1
Pulmonary infarct	0	1	0	1
Renal thrombosis	1	0	0	1
Meningitis	1	0	0	1
Bacterial endocarditis	1	0	0	1
Aseptic necrosis of the head of the femur	0	1	2(?)	1(2?)

Rheumatic heart disease and "jaundice and fever," which are included in the tabulation of complications by Duckett and Davis,[44] are not mentioned here. The jaundice and fever, obviously signs of a crisis, certainly must have occurred more frequently than the four times noted in the literature. As for rheumatic heart disease, we feel that it is diagnosed too frequently in conjunction with sickle-cell disease and is not demonstrated pathologically. We fully realize, however, that it is often impossible to rule it out clinically; for example, 4 of the 9 patients in our series had this diagnosis at one time or another. In reviewing the 24 cases which underwent autopsy no evidence of this condition was found.

Maternal Mortality.—There were 30 deaths among the 138 women, a mortality rate of 21.7 per cent. Computed on the basis of 286 total gestations, the rate was 10.5 per cent. In other words, the danger of maternal death increases with each succeeding pregnancy.

Table IV is an analysis of the 30 deaths. The second death apparently was as much the result of the shock following prolonged labor and cesarean section as of sickle-cell disease. Deaths 3, 10, 18, and 19 were due primarily to severe infection; the last of these deaths occurred in 1947, and it is probable that we have better control of similar infections at present. Another death (No. 17) was due to extensive tuberculosis with sickle-cell disease only a contributing factor. Deaths 12 and 15 terminated as uncontrollable eclampsia, and the role of the sickle-cell disease here is not clear.

In the remaining 22 cases the cause of death was sickle-cell disease. Thirteen of these patients died suddenly, usually complaining of extreme dyspnea. Six of these died undelivered. The other 7 had spontaneous deliveries (3 stillborn infants) and were apparently well up to a short time before death. The course of the 9 other patients varied, with pulmonary symptoms predominating.

In all, 11 of these patients died undelivered, and 5 more had viable but dead infants. Eleven babies survived, and 2 mothers died after abortions. In one case the fate of a viable baby was not mentioned. Of the 11 undelivered patients, 8 deaths occurred between the twenty-fourth and thirty-second weeks of gestation; 2 at term; and one in a patient only 18 weeks pregnant following pyelonephritis. These figures may be of significance in deciding the value of therapeutic abortions or induction of labor.

Pathologic Findings.—Six of the 30 patients were not subjected to autopsy, and 8 of those who were showed no major pathologic condition other than sickle-cell anemia. Six others had other pathologic findings as the chief cause of death (tuberculosis and renal infections). Seven cases showed widespread thrombotic manifestations in the lungs, spleen, kidneys, liver, pelvis, and brain. Unfortunately brain examination was not done in all cases. Two showed heart failure as well as sickle-cell disease. In one case a complete autopsy was not done after the sickle-cell anemia had been diagnosed from a blood specimen of the cadaver.

Fetal Loss.—Table V shows the fetal wastage and its causes. In 7 cases the outcome of the pregnancy with regard to fetal survival was not known. If these cases are omitted, the fetal wastage was 41.9 per cent. The spontaneous abortion rate was 19.3 per cent. Excluding the 3 therapeutic abortions, the salpingectomy, 11 patients who died undelivered, and the 2 cases whose outcome are unknown, 75.3 per cent of the pregnancies were viable; 22.5 per cent of these resulted in stillbirths or neonatal deaths (excluding the 5 cases the final fetal outcome of which is unknown). We know of no other maternal disease which produces such a great fetal loss.

Effect of Sickle-Cell Disease on Pregnancy

From the various statistics we know that sickle-cell disease is associated with a very high fetal wastage. Why this is so is not known. Labor is not affected by this disease, most of the deliveries being normal and spontaneous. Maternal infections (respiratory, genitourinary, and puerperal) are frequent, but they should not constitute too great a problem with the antibiotics now available. Toxemias of pregnancy occur in 10 per cent of the cases, an incidence which is greater than normal, but not inordinately so.

Effect of Pregnancy on Sickle-Cell Disease

This relationship is far more difficult to evaluate, partly because of a lack of comparative studies. It is easy to assume that pregnancy aggravates sickle-cell disease on the basis of the high maternal mortality rate and the fact that many cases are detected for the first time during pregnancy. On the other hand, many investigators believe that numerous patients with sickle-cell disease go through pregnancy with the disease in the latent phase, innocuously and undiagnosed. Also, one case has been reported in which the leg ulcers of a woman with sickle-cell disease cleared up during pregnancy with recurrence following delivery; the sickle-cell disease was actually ameliorated during the pregnancy.[38]

We will be in a better position to weigh the effect of pregnancy on sickle-cell disease when we make the diagnosis more frequently in asymptomatic patients, as well as in those in crisis. A comparison between groups of preg-

TABLE IV. ANALYSIS OF 30 MATERNAL DEATHS

AUTHOR	YEAR	AGE	CLINICAL COURSE	AUTOPSY FINDINGS
1. Yater and Mollari[1]	1931	25	Died in "abdominal crisis" 3 weeks after spontaneous abortion in twenty-seventh week of gestation	Sickle-cell anemia; infarcts of spleen and kidney; hypertrophy and dilatation of heart, "abdominal crisis"; large liver, small spleen
2. Lash[2]	1934	21	Died 6 hours after cesarean section for cephalopelvic disproportion; had hypertension	Postoperative shock, sickle-cell disease; large liver and spleen
3. Killingsworth and Wallace[5]	1936	28	Died 6 weeks post partum	Puerperal infection
4. Reid[6]	1936	?	Sudden death 4 days post partum	Sickle-cell anemia; large spleen, slightly enlarged liver
5. Reid[6]	1936	?	Sudden death, undelivered, in twenty-eighth week of gestation	Sickle-cell anemia; large spleen, slightly enlarged liver
6. Reid[6]	1936	?	Sudden death, undelivered, at term	Sickle-cell anemia; large spleen, slightly enlarged liver
7. Page and Silton[9]	1939	20	Died undelivered in twenty-fourth week of gestation; diagnosis of bronchopneumonia	Thrombophlebitis of pelvic veins with multiple pulmonary emboli; sickle-cell anemia; spleen small
8. Kobak, Stein, and Daro[10]	1941	22	Died 6 hours after delivery at term; treated for pneumonia	Sickle-cell anemia; atelectasis and pulmonary congestion; liver and spleen large
9. Noyes[13]	1946	32	Died undelivered in twenty-eighth week of gestation, 1½ hours after induction with Voorhees bag because of toxemia and congestive failure	Sickle-cell anemia; right-sided heart failure with pleural effusion; large spleen and liver
10. Carangelo and Otts[17]	1947	20	Died 12 hours after premature delivery at thirty-sixth week of gestation; had toxemia and fever	Bilateral renal abscesses and overwhelming kidney infection; large spleen and liver
11. Fouché and Switzer[23]	1949	19	Sudden death, undelivered, in twenty-eighth week of gestation, preceded by marked dyspnea	Sickle-cell anemia; myocardial degeneration, dilatation and hypertrophy; thrombi in heart, lungs, and kidney; large liver, small spleen

12. Fouché and Switzer[23]	1949	16	Entered hospital with toxemia; became comatose and died, undelivered, in thirty-second week of gestation	Sickle-cell anemia; myocardial dilatation and hypertrophy; hydrothorax, hydropericardium, ascites; pulmonary and generalized edema; liver and spleen enlarged
13. Fouché and Switzer[23]	1949	22	Delivered a live premature baby in thirtieth week of gestation, had crisis and died on second postpartum day	No autopsy
14. Fouché and Switzer[23]	1949	25	Admitted with marked dyspnea and pulmonary edema 4 hours after home delivery at term; died on fourth postpartum day	No autopsy
15. Rigdon[24]	1949	17	Died at term undelivered, in toxemia and convulsions	Sickle-cell anemia; subarachnoid hemorrhage; thrombi to brain and lungs; liver enlarged, spleen atrophic
16. Mueller, Bila, and Lapp[26]	1950	17	Died suddenly shortly after delivery at term; clinical diagnosis of pulmonary embolism secondary to femoral thrombophlebitis	No autopsy
17. Beacham and Beacham[31]	1950	25	Died "in shock" 3 hours after a prolonged labor at term	Spleen small; sickle-cell anemia not cause of death; tuberculosis of spine with iliopsoas abscess; massive pulmonary thrombosis
18. Beacham and Beacham[31]	1950	18	Died in sepsis 5 days after a full-term delivery, following prolonged labor	Sickle-cell anemia; overwhelming uterine and urinary infection; spleen large
19. Beacham and Beacham[31]	1950	30	Died "in shock" 1 hour after premature delivery in thirty-first week of gestation; patient in emaciated state due to resistant pyelonephritis	Sickle-cell anemia in crisis; resistant pyelonephritis; pyoarthrosis, bacteremia; spleen small
20. Beacham and Beacham[31]	1950	32	Died suddenly "in shock" undelivered in twenty-fifth week of gestation, on medical service	Sickle-cell anemia in crisis; thrombi in pulmonary arteries; large liver and spleen

TABLE IV—CONT'D

AUTHOR	YEAR	AGE	CLINICAL COURSE	AUTOPSY FINDINGS
21. Edington[34]	1951	21	Died suddenly undelivered in twenty-eighth week of gestation after complaining of dyspnea and weakness	Sickle-cell anemia; large spleen and liver; no thrombi in heart or brain
22. Edington[34]	1951	20	Died undelivered in twenty-eighth week of gestation after complaining of dyspnea, becoming delirious, and collapsing	Sickle-cell anemia; large spleen and liver; no thrombi in heart or brain
23. Daniel, Caruso, and Siegelbaum[36]	1951	19	Died suddenly on fourth postpartum day after delivery in thirty-second week of gestation, complaining of dyspnea and severe abdominal pain	No autopsy
24. Charet, Waltman, and Fernbach[37]	1952	26	Sudden death about 5 to 6 hours after delivery of stillborn infant in thirty-second week of gestation	Sickle-cell anemia; thrombosis of ovarian veins, massive pulmonary artery embolus
25. Wyatt and Orrahead[39]	1952	27	Admitted in coma in thirty-sixth week of gestation with dyspnea; dyspnea increased after a spontaneous delivery and patient died within 24 hours post partum	Sickle-cell anemia; massive fat embolism from bone marrow infarction due to sickle-cell thrombi; emboli in brain, lungs, liver; liver and spleen enlarged
26. Fouché and Williamson[42]	1953	15	Eclampsia prior to delivery at term; eclampsia improved after delivery, but patient went into crisis and died on sixth post partum day	No autopsy
27. Winston and Mastroianni[43]	1953	17	Admitted with pre-eclampsia in thirty-sixth week of gestation; died suddenly 8 to 10 hours after premature delivery	Sickle-cell anemia; large spleen
28. Duckett and Davis[44]	1953	27	Died undelivered in eighteenth week of gestation following pyelitis	Old tuberculosis; chronic pyelonephritis; large liver, small spleen; death due to "acidosis"
29. Duckett and Davis[44]	1953	18	Died suddenly 1½ hours after delivery of stillborn infant in thirty-second week of gestation; death probably due to embolism	No autopsy
30. Harlem Hospital	1955	18	Died suddenly 5 hours after delivery of stillborn infant in twenty-eighth week of gestation	Sickle-cell anemia; complete autopsy not done

nant and nonpregnant women with sickle-cell disease over an equal period of time would also help in determining the relationship between these two conditions. For the present, concrete evidence that pregnancy exerts any specific deleterious effect on the course of sickle-cell disease is lacking.

TABLE V. CAUSES OF FETAL LOSS

CAUSE	NUMBER
Spontaneous abortions	55
Therapeutic abortions	3
Salpingectomy	1
Mothers died undelivered	11
Stillborn and neonatal deaths	47
Total	117

Fertility of Women With Sickle-Cell Disease

The lower incidence of sickle-cell disease among pregnant women, as compared to the general population, has led to the impression that women with the disease are relatively infertile. Actually there is no real proof of this.

In the 138 cases reported, there were 286 pregnancies, an average of slightly more than 2 pregnancies per woman. This incidence would have been higher had not 30 of these women died during pregnancy. Also in several cases it is not known whether or not there had been previous pregnancies. In addition, some of these women were sterilized or had had other gynecologic procedures which ended their childbearing ability.

Several reasons can be advanced to explain the low incidence of sickle-cell disease among the pregnant. In the first place, all pregnant Negroes with anemia are not investigated for sickle-cell disease. Many are given iron medications or transfusions and do well thereafter, without the true nature of their anemia being discovered. Second, many women with sickle-cell disease are chronic invalids by the time they have reached the childbearing age and do not engage in normal sexual relations. Finally, the incidence of sickle-cell disease is probably lower in all Negroes in the childbearing age than in the general population, since many with the disease die before they reach that period of life. A study of the incidence of sickle-cell disease in nonpregnant Negroes in the same age group as the pregnant ones with the disease (16 to 35 years) would shed light on this question.

Management of the Pregnant Woman With Sickle-Cell Disease

During the prenatal period weekly hematologic examinations should be performed, and vitamins, iron, and liver extract should be given. Cobalt has been used in a few cases with encouraging results.[64] Transfusions are not indicated in the patient not in crisis unless the hemoglobin is less than 8 Gm.[61]

Should the patient go into crisis or develop a respiratory or genitourinary infection, immediate hospitalization and treatment with antibiotics and transfusions are mandatory. These patients are notoriously prone to develop transfusion reactions and must be watched closely. ACTH and cortisone have been

used in treating the crisis of sickle-cell disease with good results.[65] Oxygen for dyspnea and prophylactic digitalization for impending heart failure are utilized.

Many authors advocate induction of labor, when the fetus is viable, for fetal salvage.[23, 45, 46] As yet, there is no definite evidence that this procedure has produced more live babies. At Harlem Hospital in the past we have allowed our patients to deliver spontaneously. In a case near term with a "ripe" cervix or ruptured membranes, we probably would attempt induction.

Labor is managed along conventional obstetric lines. Oxygen should be given freely to these patients, and prophylactic low forceps delivery under pudendal block is the desirable method. Antibiotics are also given prophylactically at the onset of labor and are continued through the puerperium.

Cesarean section is reserved exclusively for obstetric indications and not for fetal salvage, as it might be utilized in a diabetic patient. Section could conceivably initiate a fatal crisis. Five sections have been performed in the past in patients with sickle-cell disease.[2, 30, 32, 33, 46] The indication in 4 of the cases was cephalopelvic disproportion; in the other case the indication was not clear. One of these patients succumbed postoperatively.

Therapeutic Abortions and Sterilization.—Fouché, Switzer, and Williamson[23, 42] are advocates of therapeutic abortion early in pregnancy, especially if the patient has a history of frequent crises. Their justification lies in the very high fetal and maternal mortality rates, and these figures are incontrovertible. Further support of their contention is the fact that none of the deaths so far reported occurred in the first trimester. The risk of such a procedure should, therefore, not be great.

On the other hand, Beacham and Beacham[61] stated that sickle-cell disease per se is not an indication for therapeutic abortion. The difference of opinion is due to the fact, as previously noted, that we do not know how pregnancy affects sickle-cell disease if at all. Once a pregnancy has occurred, it is reasoned that it should be allowed to continue, especially if the fetus is "valuable." Our policy at Harlem Hospital is not to perform therapeutic abortions.

Sterilization has not been performed often in the past, but it will probably be done more frequently as more cases are recognized and as these patients go through repeated pregnancies. The high maternal mortality rate, which increases with each pregnancy, certainly justifies this procedure. In addition, Beacham and Beacham[61] have made the point that these mothers seldom live long enough to raise their children.

Summary and Conclusion

1. The literature on sickle-cell disease in pregnancy has been reviewed, and 9 additional cases have been reported. This makes a total of 138 known cases with 286 pregnancies.

2. Thirty of the mothers in this series died during or shortly after a pregnancy, a gross mortality rate of 21.7 per cent. The mortality rate per individual pregnancy was 10.5 per cent.

3. The total fetal mortality was 41.9 per cent, and the spontaneous abortion rate was 19.3 per cent. Of the pregnancies which reached the stage of viability 22.5 per cent terminated as stillbirths or neonatal deaths.

4. Sickle-cell disease has little or no effect on labor. Its greatest effect is on the fetus. It is also associated with increased maternal infections.

5. The effect of pregnancy on sickle-cell disease has not been clearly established up to the present time.

6. Infertility in women with sickle-cell disease is more apparent than real.

7. The treatment of sickle-cell disease in pregnancy has been discussed.

8. Sickle-cell disease is not an indication for therapeutic abortion. Sterilization should be considered, however, in women who already have children.

9. Physicians should have a "high index of suspicion" for this disease in anemic Negroes or in those with bizarre symptomatology.

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THE CLINICAL DETERMINATION OF PELVIC OUTLET CAPACITY

An Adjunct to the Roentgenometric Survey of the Upper Pelvis

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THE purpose of this communication is to demonstrate that the bony pelvic outlet can be surveyed with reasonable accuracy by clinical methods and that they can serve as an adjunct to x-ray techniques used for surveying the pelvis above this level. In combination with the single inlet and single lateral film of the Thoms-Wilson technique,[1] these clinical techniques will establish dimensional and morphological data suitable for adequate pelvic assessment. We are convinced that such a survey should be part of the antenatal record of every primigravid woman.

Experience in evaluating outlet capacity by both clinical and x-ray techniques has shown that rather well-established outlet measurements do not have the usefulness in expressing outlet capacity that is essentially desired. We refer to *A*, the determination of the subpubic angle; *B*, the intertuberal dimension (outlet transverse); and *C*, the posterior sagittal diameter of the outlet. The measurement of the subpubic angle is not a reliable index of spatial value of the pubic arch, as is demonstrated in Figs. 1 and 2. The intertuberal dimension is too much influenced by subjective variations due to lack of definitive end points. As a result, the posterior sagittal diameter also may not give reliable information. The determination of the outlet *anteroposterior diameter* as here defined, with the determination of the *available (corrected) anteroposterior diameter* in instances of abnormally narrowed pubic arch, is the most satisfactory index to outlet capacity.

It is important to consider influences which may modify to some extent mensuration in this part of the pelvis. We refer to the effect that mobility, or give, of the pelvic joints may have on outlet capacity. Because of mobility, body posture can considerably influence the symphysiosacral relationships, and thereby increase or decrease the outlet anteroposterior diameter. All the pelvic joints show increased relaxation under the influence of pregnancy. Relaxation of the symphysis is a progressive phenomenon as we have previously shown.[2] The influence of posture in affecting outlet capacity has been known for a long time. Our own studies[3] of the effect of the exaggerated lithotomy position on the outlet anteroposterior dimension showed that in 80 per cent of the 500 pregnant women this diameter was increased 1.0 cm. or more, in 20 per cent of whom the increase was 1.75 or more.

This entire question of joint relaxation in pregnancy deserves further study by modern roentgen techniques. Brook,[4] writing in 1934, stated that pregnancy

in the female at full term increases sacroiliac mobility two and one-half times above the maximum degree present in the nonpregnant woman of the same age.

The *anteroposterior diameter of the outlet,* as we employ it, represents the distance from the lower margin of the symphysis to the lowest fixed sacral or coccygeal segment (usually the tip of the sacrum) (Fig. 4). When abnormal narrowing of the pelvic arch is present to a degree which denies to the head anterior space in the arch, the anteroposterior diameter is no longer a true index of outlet capacity (Fig. 3). Truer perspective is seen in the so-called *available (or corrected) anteroposterior diameter,* which is the distance extending from a hypothetical pubic arch to the posterior end point mentioned. Thus, when the subpubic arch is wide, the available anteroposterior diameter will be the same as the anteroposterior diameter; but when the arch is narrowed, the available anteroposterior diameter will be shorter and will lie in a lower pelvic plane (Figs. 3 and 4).

Fig. 1.

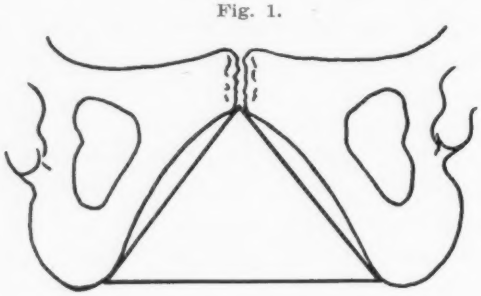
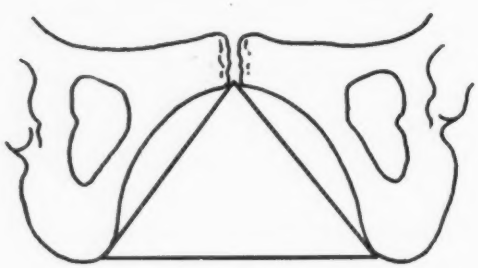


Fig. 2.



Figs. 1 and 2.—The pubic angles and bituberal distances are identical. The pubic arches, however, have important differences from the obstetrical viewpoint. (From Thoms, H.: Surg., Gynec. & Obst. 83: 399, 1946.)

Williams and Arthure,[5] who have studied these relationships roentgenologically, stated, "When the descending pubic rami show a marked posterior inclination and the subpubic arch is narrow, then there will be the greatest difference between the anatomical and the available anteroposterior diameter of the outlet. Differences between these two measurements of as much as 1.8 or 2.0 cm. were found in our material."

We believe that either of these diameters can be determined with reasonable accuracy with the use of the metal ring gauge and calipers, here described

(see Fig. 5). The idea of a metal gauge to determine a hypothetical pubic arch is adapted from W. I. C. Morris[6] who uses a solid metal gauge of smaller dimension (8.0 cm.). This author said, "This is a much more accurate method of evaluating the obstetrical calibre of the pubic arch than any of the standard subjective estimations depending simply on palpation, and at the very least it enables the obsetetrician to detect the cases in which the pubic arch requires radiological investigation."

We believe the ring gauge of 8.5 cm. diameter, fitted under the pubic arch with the woman in the lithotomy position (Fig. 6), is of aid in establishing the proper anterior end point for measuring the available anteroposterior diameter in instances of narrowed arch. The gauge represents the suboccipitobregmatic circumference (average diameter 9.5 cm.). In using a gauge with an 8.5 cm. diameter, we are allowing 1.0 cm. for the thickness of the soft tissue overlying the descending pubic rami. As will be seen, the gauge has a 5.0 cm. scale projection at its edge. The ring gauge is made of aluminum or magnesium, 0.5

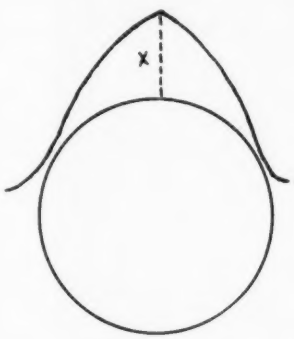


Fig. 3.

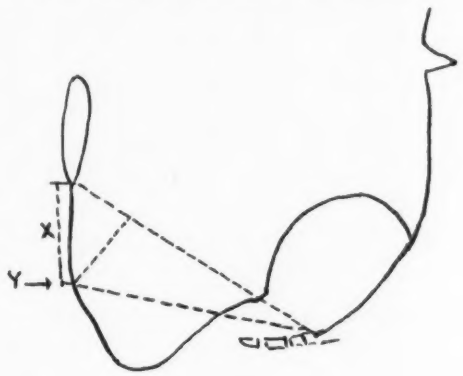


Fig. 4.

Fig. 3.—Space at x is unavailable space in instances where the fetal head is forced posteriorly, because of narrow arch.

Fig. 4.—End point of available anteroposterior diameter is at point y. Line x represents unavailable space shown in Fig. 3.

cm. in thickness, with rounded edge. At the examination, the gauge is fitted into the arch with the free edge upward. Separation of the soft tissues on either side by the examiner's free hand aids in slipping the gauge under the arch as close to the symphysis as possible. If there is more than 1.0 cm. distance between the ring gauge and the symphysis, a distance measured by reversing the position of the gauge, using the scale against the symphysis, the available anteroposterior diameter is determined.

For purposes of illustration, assume an instance in which this distance is 3.0 cm. This would mean that the available anteroposterior diameter must be measured from a hypothetical point in the midline in the plane of the inner borders of the descending rami, at a point 3.0 cm. below the symphysis. The establishment of the *anteroposterior diameter* or, in instances of narrow arch, the *available anteroposterior diameter* is accomplished as follows: first the position and mobility of the coccyx are established, determining the *lowest fixed seg-*

ment in the sacrum or coccyx. This is done by rectal examination combined with external palpation of the coccyx in the natal cleft. The coccyx then lies between the forefinger internally and the thumb externally. This determination may be made vaginally but there are instances in which identification is more assured by the rectal technique as described.

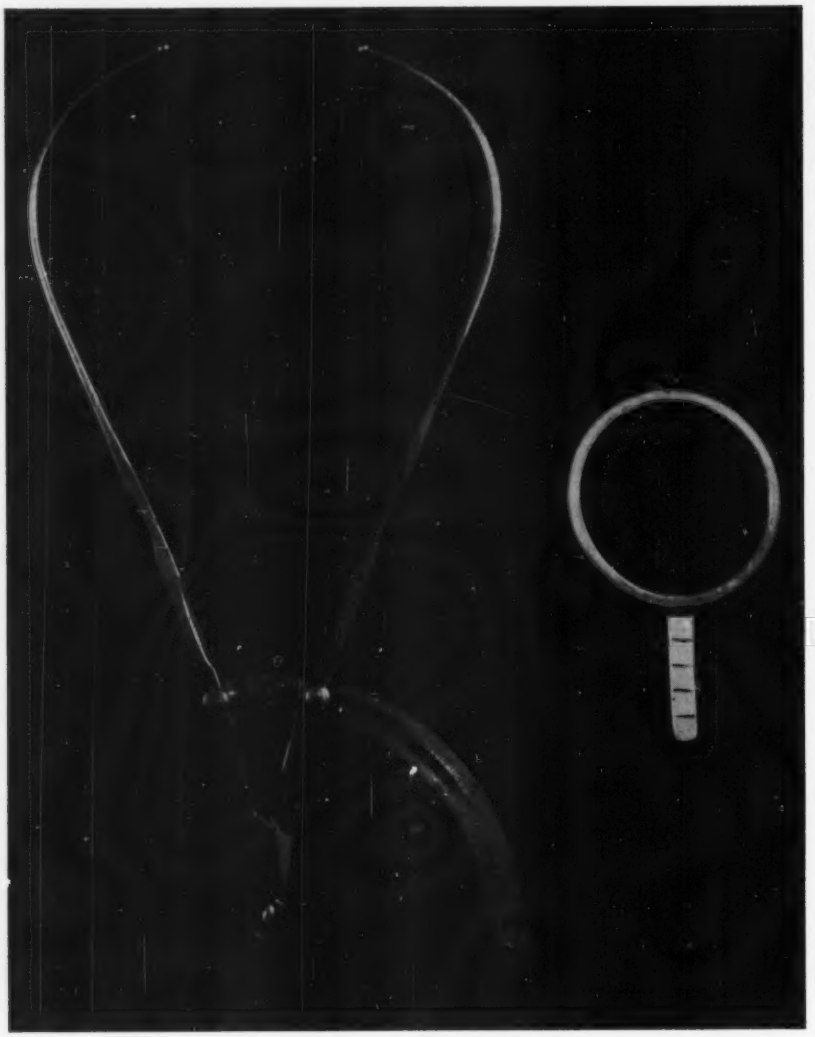


Fig. 5.—Photograph showing external pelvimeter (used as calipers) and metal ring gauge.* Measurement between caliper ends is made directly on a centimeter scale.

The position of the lower edge of the lowermost fixed sacral segment having been established, an identification mark is made on the skin opposite in the natal cleft. The *anteroposterior* diameter is measured by the calipers from a point in the midline at the lower margin of the symphysis to the marked point previously selected in the natal cleft. Measurement between the tips of the

*Manufactured by the Torrington Brush Co., Torrington, Conn.

calipers is made directly on a centimeter scale with 1.0 cm. deducted for the thickness of the sacrum and soft tissues. This measurement may be determined vaginally with the forefinger of the examining hand in contact with the posterior end point (Fig. 7) and the base of the forefinger against the lower edge of the symphysis (as in the well-known diagonal conjugate maneuver) measuring the intervening distance on a centimeter scale. Morris[6] said that the internal measurement can be made with accuracy very close to the radiological measurement, and Heyns[7] claimed that the external method is at least as accurate as the x-ray measurement if deduction of 1.0 cm. is made. For routine purposes we believe the external method is preferable because of the ease with which the posterior end point can be identified.

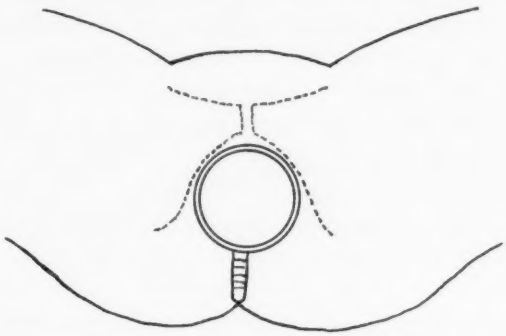


Fig. 6.—The metal ring is fitted externally under the pubic arch in a line with the descending rami.

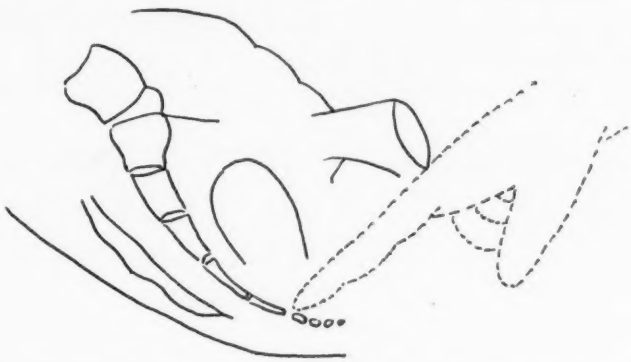


Fig. 7.—Measurement can be made internally with the forefinger as in the "diagonal conjugate" maneuver.

In determining the *available anteroposterior diameter* in instances of narrowed arch, fitting the metal ring gauge under the pubic arch establishes the anterior end point at the top of the ring. The ring is steadied in position by an assistant and the tip of the anterior area of the calipers is brought to the top of the circle. The establishment of the available anteroposterior diameter is the best index to outlet capacity, but we would point out that in all pelves with abnormally narrowed arches the added knowledge of the midplane transverse dimension (interspinous) as determined roentgenologically is essential for satisfactory prognosis.

Outlet contraction may manifest itself as:

1. Abnormal shortening of the anteroposterior diameter as a part of a general funnel tendency in which transverse shortening of the midplane (interspinous distance) is also present.

2. Transversely alone by too prominent ischial spines.

3. Anteroposteriorly alone by unusual convergence forward of the lower sacrum.

4. Narrowing of the pubic arch alone.

The dictum of Morris[8] is probably the final word in consideration of the anteroposterior diameter as the best index to outlet capacity. He stated that, "if the anteroposterior diameter of the plane of least pelvic dimensions measures 11.5 centimetres or more, serious anteroposterior narrowing of the outlet can be ruled out, since in the narrowest pelvic arches the corrected (available) anteroposterior diameter very seldom differs more than 1.5 centimetres from the anteroposterior diameter of the inferior strait."

Summary

1. Clinical methods of examination can be relied upon to furnish an estimation of pelvic outlet capacity and serve as an adjunct to the general x-ray survey of the pelvis.

2. The anteroposterior diameter of the outlet, or in specific instances the available anteroposterior diameter, is the best single index to outlet capacity.

3. An adequate general pelvimetric survey can be accomplished by the use of two films, one inlet view and one lateral view, plus clinical assessment of the pelvic outlet as here described.

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AN ELECTIVE PROGRAM ON PREPARATION FOR CHILDBIRTH AT THE SLOANE HOSPITAL FOR WOMEN, MAY, 1951, TO JUNE, 1953*

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THIS report is based upon the attitudes, feelings, and reactions of doctors and nurses and people from many departments in Columbia-Presbyterian Medical Center who have worked with parents and helped to develop the preparation for childbirth program. It also reports some of the subjective and clinical results in childbirth.

A number of mothers who planned to have their babies in Sloane Hospital had asked for classes in preparation for childbirth, with emphasis on natural childbirth. Members of the obstetrical staff were interested in setting up a plan to meet the needs of these mothers. A committee was also interested in knowing how many mothers registered at the maternity clinic would elect to attend preparation for childbirth conferences if the service were offered to them.

The project was planned as follows: Eleven unselected new registrants in the antepartal clinic were interviewed every week and asked if they would like to attend the classes. Approximately eleven new registrants are admitted to the antepartal clinic every day, or a potential quota of fifty-five patients per week. A record was kept of all mothers interviewed, in two categories: (1) the unselected mothers registered at the Maternity Clinic who accepted the program, and (2) those who chose not to attend, who were ineligible, or who registered for classes but failed to attend. A record was also kept of clinic and private patients who requested the instruction and attended the conferences.

Selection of Patients (Table I)

All parents were not interested in receiving preparation for labor. Of the 742 unselected clinic patients interviewed, 515 (69.4 per cent) expressed interest in the preparation for childbirth conferences. The remainder, 30.6 per cent, chose not to attend the conferences. Most of these were too busy, or could not find "sitters" for their other children. Others were not sufficiently interested to attend the conferences, or were unable to speak English. Thus 283 of the 742 patients interviewed attended the conferences.

There was an additional group of 249 who came seeking instruction. These were women who had heard of "preparation for childbirth" or "natural childbirth," or had attended classes elsewhere during previous pregnancies. This is a selected group in that the interest was already aroused.

A graduate nurse-midwife, who had been a Maternity Center Association Fellow in the natural childbirth demonstration conducted by the Association and Yale University at the Grace-New Haven Hospital, was appointed to con-

*This project was sponsored jointly by Presbyterian Hospital, Maternity Center Association, and New York Foundation.

duct the study. Her first task was to become acquainted with the staff, the procedures, and the attitudes toward parents in all units of the maternity service.

TABLE I. SELECTION OF PATIENTS FROM MAY 8, 1951, TO FEB. 15, 1953

		NO.	%
	742 Patients Interviewed		
I.	Total number of unselected clinic patients who expressed interest in the education for childbirth program	515	69.4
	a. Number of unselected clinic patients medically disqualified or unable to communicate in English	153	20.6
	b. Number of patients reclassified during pregnancy—*did not keep* appointments	79	10.7
	c. Number of unselected clinic patients who attended one or more conferences 229	283	38.1
	d. Number of unselected clinic patients currently attending conferences 54		
II.	Total number of unselected clinic patients who chose not to attend conferences	227	30.6
	a. Preferred to be asleep when their babies were born	13	1.8
	b. Not interested in attending conferences or "too busy"	77	10.4
	c. Unable to leave other children	137	17.1
III.	Total number of private and clinic patients who requested instruction	249	33.6

Many of the supervisors and members of the nursing staff had already been to the Maternity Center Association for instruction in applying the principles of relaxation to mothers in labor. They welcomed the opportunity for other members of the staff to receive this preparation.

The Conferences

The program in preparation for childbirth began with a series of six 1½ hour conferences with the mothers; later mothers and fathers were taught together. These conferences were parent-centered and the attempt was made to answer all questions asked. Emphasis was placed upon the fact that having a baby is one of the natural functions of living.

Six conferences, by the best standards, are not enough to give to each mother and father a feeling of confidence and security which springs out of a good knowledge of the childbearing process.

The discussions in this demonstration were focused on labor and on teaching the mother and father how they would participate actively with the doctor and nurse in the actual coming of their baby. A lesson plan was worked out for each conference session, but questions on any subject relating to childbearing were answered whenever asked, whether the question fitted the lesson plan or not.

Management of Labor

When labor actually begins and the mother is admitted to the hospital, both parents know what to expect. The husband waits outside the delivery room suite until all routine procedures are completed and then he is given a cap, gown, and mask and invited into the labor room. Labor rooms are all single rooms and continuous nursing support is provided while the mother is in labor. For diversion, the husband many times reads to or plays cards with his wife, or they may listen together to their favorite radio program. The labor rooms are supplied with individual ear phones for this purpose.

When an obstetrician comes into a labor room to make an examination, our patients usually cooperate intelligently. They have been taught the con-

trast between relaxed and tense muscles and they understand why the examinations are made. They expect to follow the progress of their labor and appreciate being informed of any progress that has been made in the dilatation of the cervix. They are encouraged and pleased when they discover that they can apply what they have learned in class.

When they are having strong contractions, they do controlled breathing with the contractions and rest between them. They assume any position that is comfortable, such as the relaxation position on their backs, on their sides, or on all fours.

Some patients preferred to be left with their obstetrician and nurse and had their husbands wait at home. Others desired to be very quiet in labor, doing the controlled breathing without any reassurance that they were doing well. Some needed frequent regular encouragement. Some mothers wanted to watch their babies while they were being born. Others preferred to be asleep. Some mothers wanted to hold their babies immediately after they were born. Others said they were too tired from the hard work and preferred to admire them in the crib.

Evaluation of Results (Table II)

The philosophy of natural childbirth is explained and discussed. It is made clear to every parent that there is no such thing as success or failure. Each person is an individual with certain basic emotional and physical characteristics. The function of the natural childbirth program is to help each parent develop her strengths to the fullest and the only evaluation of success is whether or not a mother is satisfied with her experience.

It has been difficult to select criteria. Menninger[1] has stated "we should take more time and listen to the patient's story" and that every case has three diagnoses: physical, psychological, and social. In the labor room we have provided an evaluation record. The obstetrician answered the following questions:

a. Was the mother controlled throughout labor?
Note: Check successful, reasonably successful, fairly successful, or unsuccessful.
b. Was she completely cooperative throughout?
c. Was she pleased with her delivery?
d. Was she happy with her baby?

We have asked patients the following questions:

a. Are you satisfied with your experiences?
b. Would you elect natural childbirth next time?
c. When did you experience the greatest degree of pain or discomfort?
d. Are you happy with your baby?

TABLE II. CRITERIA OF SUCCESS

	MOTHERS	OBSTETRICIANS
230 Evaluation Records Reviewed		
Successful	142	150
Reasonably successful	46	24
Fairly successful	32	24
Unsuccessful	10	27
Not evaluated		5
Obstetricians scored higher than mothers' evaluations in 35 records.		
Obstetricians scored lower than mothers' evaluations in 30 records.		

Length of Labor.—Van Auken and Tomlinson[5] in their study of 400 primiparous patients (one half used as controls) reported, "From the study it is evident that labors are shortened by at least 2 hours." "Length of labor in the trained group 13.5 hours—control group 15.5 hours."

Thoms and Wyatt[4] reported:

For primiparas: mean average, 14.3 hours median, 11 hours
For multiparas: mean average, 8 hours median, 6.96 hours

In primiparas the shortest length of labor was in the private group, 9 hours, 50 minutes, compared with 11 hours, 33 minutes, in the unselected clinic group of patients who did not attend classes.

In multiparas the shortest length of labor was in the clinic unselected prepared group of patients, 7 hours, 37 minutes, compared with 8 hours, 55 minutes, in the private group and 8 hours, 25 minutes, in the patients who did not attend conferences.

Types of Delivery (Table III).—We reviewed 573 charts of patients who had been delivered to determine the types of delivery; spontaneous, low forceps, midforceps, and cesarean section.

TABLE III. TYPES OF DELIVERY

	GROUP I UNSELECTED CLINIC PATIENTS WHO ATTENDED THE CONFERENCES		GROUP II UNSELECTED CLINIC PATIENTS WHO DID NOT ATTEND CONFERENCES		GROUP III REQUEST CLINIC AND PRIVATE PATIENTS	
	NO.	%	NO.	%	NO.	%
573 Charts Reviewed						
Primiparas (286).—						
a. Spontaneous vertex	30	42.3	28	36.4	76	55.1
b. Low forceps	29	40.9	38	49.4	43	31.2
c. Other operative deliveries	12	16.9	11	14.3	19	13.8
Total	71	100.0	77	100.0	138	100.0
Multiparas (287).—						
a. Spontaneous vertex	18	72.0	153	68.0	33	89.2
b. Low forceps	6	24.0	39	17.3	4	10.8
c. Other operative deliveries	1	4.0	33	14.7	0	0.0
Total	25	100.0	225	100.0	37	100.0

Blood Loss (Table IV).—The blood loss in patients who attended the preparation for childbirth conferences was approximately the same as that in the unselected clinic group who did not attend conferences. The numbers are too small to be of any real significance.

Analgesia (Table V).—Thoms and Wyatt[4] in their report stated that in 214, or 73.3 per cent, of the spontaneous deliveries in primiparas not over 125 mg. of Demerol or one dose of another agent was used. In 19.9 per cent (primiparas) there was no analgesic. In 530, or 89.9 per cent, of the spontaneous deliveries in multiparas not over 125 mg. of Demerol or one dose of another agent was used. In 49 per cent (multiparas) there was no analgesic.

The amount and type of medication needed by patients who attended our conferences on preparation for labor were very similar to those reported by Thoms and Wyatt.

In those who had medication, appreciably less was required in Groups I and III (Table V). Medication was always offered whenever the patient showed any sign of stress or increasing discomfort. We have not been able

to prove that any harm was done by the medication in Group II, but many have the impression that a decrease in the amount of medication will be of definite value to the baby.

Anesthesia (Table VI).—The prepared patients required much less anesthesia than the women who did not attend conferences. Again, anesthesia was offered to all patients.

TABLE IV. BLOOD LOSS

AMOUNT OF BLOOD LOST (C.C.)	GROUP I UNSELECTED CLINIC PATIENTS WHO ATTENDED THE CONFERENCES		GROUP II UNSELECTED CLINIC PATIENTS WHO DID NOT ATTEND CONFERENCES		GROUP III REQUEST CLINIC AND PRIVATE PATIENTS	
	NO.	%	NO.	%	NO.	%
			550 Charts Reviewed			
Primiparas (252).—						
250 or less	43	65.2	49	52.1	79	85.9
250-499	11	16.7	15	16.0	5	5.4
500-749	1	1.5	1	1.1	2	2.2
No record	11	16.7	29	30.9	6	6.5
Total	66	100.0	94	100.0	92	100.0
Multiparas (298).—						
250 or less	23	92.0	166	65.9	19	90.5
250-499	2	8.0	23	9.1	1	4.8
500-749	0		7	2.8	0	0.0
No record	0		56	22.2	1	4.8
Total	25	100.0	252	100.0	21	100.0

TABLE V. ANALGESIA

	GROUP I UNSELECTED CLINIC PATIENTS WHO ATTENDED THE CONFERENCES		GROUP II UNSELECTED CLINIC PATIENTS WHO DID NOT ATTEND CONFERENCES		GROUP III REQUEST CLINIC AND PRIVATE PATIENTS	
	NO.	%	NO.	%	NO.	%
			448 Charts Reviewed			
Primiparas (213).—						
No medication	14	19.7	2	3.1	17	22.1
Dosage I						
Demerol 1 or 2 doses, or Seconal and Demerol	25	35.2	12	18.5	41	53.3
Dosage II						
Demerol and scopolamine	32	45.1	51	78.5	19	24.7
Total	71	100.0	65	100.0	77	100.0
Multiparas (235).—						
No medication	6	27.3	13	6.8	7	33.3
Dosage I						
Demerol 1 or 2 doses, or Seconal and Demerol	7	31.8	23	12.0	9	42.9
Dosage II						
Demerol and scopolamine	9	40.9	156	81.3	5	23.8
Total	22	100.0	192	100.0	21	100.0

TABLE VI. ANESTHESIA

	GROUP I UNSELECTED CLINIC PATIENTS WHO ATTENDED CONFERENCES		GROUP II UNSELECTED CLINIC PATIENTS WHO DID NOT ATTEND CONFERENCES		GROUP III REQUEST CLINIC AND PRIVATE PATIENTS	
	NO.	%	NO.	%	NO.	%
	479 Charts Reviewed					
Primiparas (245).—						
Group A No anesthesia, local anesthesia, nitrous oxide with contractions	37	63.8	18	27.2	83	68.6
Group B Epidural, caudal, spinal	7	12.1	27	40.9	14	11.6
Group C Asleep-cyclopropane	14	24.1	21	31.8	24	19.8
Total	58	100.0	66	100.0	121	100.0
Multiparas (234).—						
Group A No anesthesia, local anesthesia, nitrous oxide with contractions	17	68.0	71	40.6	20	58.8
Group B Epidural, spinal, caudal	2	8.0	36	20.6	2	5.9
Group C Asleep, cyclopropane	6	24.0	68	38.9	12	35.3
Total	25	100.0	175	100.0	34	100.0

Comment

As we review the progress that has been made from the time the first class was accepted until the present time, there is good evidence that natural childbirth with its emphasis on the normal and natural, on teaching, and on the development of good relationships brings together the specialists in the various departments of the hospital and helps to focus their skills and knowledge on the mother, her baby, and her family.

A program of preparation for childbirth helps to create better relationships, for when parents learn and work together, they develop a family feeling about the baby. They easily transfer this cooperation to family life with the baby at home.

At the Sloane Hospital for Women, we have found that some husbands want to be with their wives in the labor room and other husbands prefer to stay in the waiting room until their babies are born. They appreciate being able to make the decision themselves. We have received few complaints that husbands have disturbed the staff because they have been tense and apprehensive. Some doctors and nurses have felt that the husbands have contributed a great deal to the emotional support given to their wives in the labor room.

If the program in preparation for parenthood is to be continued and expanded, we believe a central planning committee is essential, with representation from the departments of obstetrics, pediatrics, psychiatry, nursing, and other related groups.

A coordinator-teacher should be in charge of the program. She should be able to function in all units of the obstetric department as special demands for her services arise, whether it be with parents in the clinic, classroom, labor, or delivery room, or with staff and administrative heads.

Statistical data obtained from the patients' charts we reviewed have been presented.

Summary

1. The length of labor was approximately the same in all three groups.

2. There were more spontaneous deliveries in the prepared group. The highest number was in the private prepared group.

3. Appreciably less predelivery medication was requried in prepared patients.

4. An impressive number of both multiparas and primiparas required no predelivery medication.

5. The largest number of patients who required little or no anesthesia was in the group who requested the preparation classes.

Conclusions

1. In this large clinic with a high percentage of non-English speaking persons, the number suitable for this program may be small. With the exclusion of this group and the subsequent dropping of patients for medical reasons and failure to attend, only 38 per cent can be completely prepared under present circumstances.

2. A definite and increasing group of women is now applying for these classes.

3. The results of subjective evaluation of the procedures by patient and obstetrician are very good.

4. The objective criteria (blood loss, length of labor, use of instruments, etc.) are difficult to evaluate. However, definitely less analgesia is needed, perhaps partly because of the improved orientation of the patient.

5. It may be argued that the use of less analgesia would be of value to the baby.

6. This program fills a big need in the general preparation of the patient, which will be manifested in less anxiety and more intelligent cooperation than can be statistically measured.

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THE INCIDENCE OF CANDIDA IN OBSTETRICAL PATIENTS

History, Incidence, Diagnosis

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ONE of the most common complaints encountered in obstetrical and gynecological practice is the vaginal discharge. In years past the vaginal discharge was assumed to be part of female adulthood and motherhood. This is not true today, and more women are presenting themselves for treatment of this problem. The two pathogens which are most frequently to blame are *Trichomonas vaginalis* and *Candida albicans*. This paper will present the clinical incidence of moniliasis in one practice utilizing a specific, yet simple, cultural diagnostic tool.

History

Fungus infections of the vagina have been reported for over a century under various names. The first mention of the name Monilia was by Hill for the forms described by Michelli. According to Castellani, Wilkinson reported the presence of yeastlike organisms in the vaginal discharge as early as 1840, the year after Langanbeck discovered the fungus in cases of oral thrush. Mayer described the condition in 1862 and reported 6 cases.

Certain of the vaginal fungi belonging to the genus Candida have been proved to be pathogenic. The first successful human vaginal inoculation reported was that of Haussmann, who inoculated a pregnant patient with a vaginal discharge from an infected patient. Hesseltine, Borts, and Plass inoculated 18 females with pure cultures of Candida with successful infection taking place in 12. Many species of Candida have been identified and studied. Jones and Martin have isolated fifty-nine strains in one clinic. At the present time there is no conclusive evidence that Cryptococcus or Saccharomyces strains isolated from the vagina are pathogenic. Other species of *Candida* such as *stellatoidea, parakrusei, krusei,* and *tropicalis* will produce vulvovaginitis in the occasional case.[1]

It is a well-established fact that diabetes mellitus and pregnancy favor conditions for vaginal fungi to grow. Rediscovery of vaginal fungal infestations was brought about by the association of these processes. Since the advent of the antibiotics, there has been an apparent increase in the number of cases of fungal infections.[2-11]

Incidence

Many studies have been reported concerning the incidence of vaginal moniliasis. In the pregnant patients with symptoms the per cent of fungus

infections ranged from a low of 0.74 to a high of 66.7. In pregnant patients without symptoms the incidence ranged from 4 to 38 per cent. Summarizing the data on the gynecological patients with symptoms, the range was from 8.08 to 38 per cent. For asymptomatic gynecological patients the range of incidence was from 15.4 to 61.7 per cent.

In reviewing the limited published material, we find that there is great variation in reported incidence of moniliasis. It is difficult to come to any conclusions. It is generally thought that about 10 per cent of the female population at large harbor yeastlike organisms. The majority of these women appear asymptomatic. It has been postulated that locale of clinic, type of patients, etc., influenced the incidence of this disease. No doubt all factors contribute in some manner. One factor which probably influences the reported incidence of infection most is the method of determining the presence of fungi.

Diagnosis

The physician who treats only patients with obvious signs and symptoms misses many diagnoses of mycotic vulvovaginitis.[1] Differentiation should be made between: (a) those who harbor harmless saprophytes, (b) those who have a positive culture yet are asymptomatic, and (c) those who have positive cultures and symptoms.

The following four methods of examination have been used. Only one method continues to be routinely successful in the hands of many.

1. Fresh preparation or set mount. This procedure is superior to the stained smear and the potassium hydroxide or sodium hydroxide solution methods, but it is unreliable.

2. Intradermal skin test. This is of little or no value in determining the presence of fungi.

3. Agglutination test. This test bears little relationship to the presence of fungi in the vagina.

4. Culture technique. This has proved to be the only reliable method of diagnosis.

The culture medium most commonly employed until recently was Sabouraud's. This medium has the one disadvantage of supporting growth of other organisms besides Candida. In 1953 a new medium which would support the growth of fungi alone was developed. Members of the Candida group of fungi would grow on this medium as dark brown or jet black colonies. Incubation is not necessary but will speed the growth of the colony if desired. This medium was used as the single diagnostic tool in this study.*

By using this simple, specific diagnostic tool we were able to have all of the advantages of culture diagnosis, yet free from expensive, time-consuming techniques and personnel.

Material

This study included 668 of the 928 patients, both private and clinic admitted between Aug. 1, 1954, and Feb. 21, 1955, in early labor. In this

*The culture medium used in this study was supplied by the Ortho Pharmaceutical Corporation as Nickerson's Medium.

series of obstetrical cases 85 per cent were white, 10 per cent Negro, and 5 per cent Latin American. Clinical patients constituted 18 per cent of the total admissions while 72 per cent were private patients of the obstetrical staff of the Wichita General Hospital.

Method

Symptomatology was determined by the presence of any type of vaginal discharge prior to the onset of labor. If the patient complained in any way about the discharge, she was labeled symptomatic; otherwise she was considered to be asymptomatic.

After the perineum was prepared, a sterile applicator was inserted into the vagina. The material obtained was inoculated onto a tube of Nickerson's medium. The tubes of medium were allowed to stand at room temperature for five to seven days and examined for the presence of growth. A typical positive culture showed brown-to-black, raised colonies, easily observed by simple inspection. Differential bacteriological studies were not necessary inasmuch as Nickerson's medium will support the growth of members of the Candida species only.

Results

In Table I are summarized our findings on the routine culture of 668 obstetrical patients prior to delivery admitted to the Wichita General Hospital. There were 226 patients with positive cultures for Candida, an incidence of 33.6 per cent.

Table I. Incidence of Candida

TOTAL NO. CASES	NO. WITH POSITIVE CULTURE	% INCIDENCE
668	223	33.6

There were 115 patients who complained of vaginal discharge and showed a positive culture. One hundred eight patients who had no vaginal complaints were also positive for Candida when cultured. The incidence of Candida in the symptomatic and asymptomatic patients with positive cultures is shown in Table II.

Table II. Incidence of Symptomatology in Culture-positive Patients

TOTAL CASES	NO. WITH POSITIVE CULTURES	SYMPTOMATIC	ASYMPTOMATIC	% INCIDENCE
668	223	117		52
			106	48

Of the remaining 445 patients who had negative cultures, 214 had vaginal discharges prior to the onset of labor for which symptoms were present. None of these showed a positive culture for Candida. Two hundred thirty-one of the 445 cases were culture negative and asymptomatic. The incidence of these findings may be seen in Table III.

Table III. Incidence of Symptomatology in Culture-negative Patients

TOTAL CASES	NO. WITH POSITIVE CULTURES	SYMPTOMATIC	ASYMPTOMATIC	% INCIDENCE
668	445	214		48
			231	52

Conclusions

1. In a brief survey of the literature, the reported incidence of Candida has been erratic.

2. Of 668 obstetrical patients at term, 33.6 per cent showed positive culture on Nickerson's medium for Candida.

3. The presence or absence of a vaginal discharge in a patient at term does not indicate the presence or absence of Candida in the vaginal tract.

4. Nickerson's medium constitutes a simple and specific diagnostic tool enabling the clinician to determine accurately the presence of Candida without the use of a bacteriological laboratory.

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Department of Case Reports New Instruments, Etc.

ANOTHER CASE OF POSTABORTAL CLOSTRIDIUM PERFRINGENS INFECTION

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POSTABORTAL perfringens infections are quite uncommon; but, when present, the infection is of such severity that the combined skills of the clinician and the laboratories are required to combat it successfully. This problem was recently reviewed very completely by Godsick[3]; but we wish to report a recent case of our own because of its interest.

E. M. was a 23-year-old Negro woman, gravida iv, para ii, abortus i, admitted to the hospital on Jan. 20, 1954, with the chief complaints of vaginal bleeding, abdominal pain, vomiting, chills and fever.

Her last menstrual period had been Nov. 20, 1953. On December 27, a catheter was inserted into the vagina. It fell out the following day and was reinserted by the patient. On Jan. 1, 1954, she noted malaise, headaches, and fever but had not aborted. On January 15 she again consulted the abortionist, who reinserted the catheter for the third time. On January 17 she began to have abdominal pain and vaginal bleeding and removed the catheter. However, she also began to have many chills and vomited after each meal. At this time she consulted her family doctor who gave her some penicillin but advised her to go to the hospital in the morning if she were not improved.

Three days later on admission the patient appeared well nourished but lethargic, restless, and dehydrated. The temperature was 101° F., pulse 140, respirations 28, and blood pressure 80/50. Physical examination showed icteric scleras and abdominal hyperperistalsis with generalized muscle guarding. Pelvic examination disclosed a foul-smelling purulent sanguineous discharge with small pieces of placenta in the cervical canal; the body of the uterus was enlarged to the size of an eight weeks' gestation, soft and anterior. There was bilateral parametrial tenderness but no masses.

Laboratory studies showed: hemoglobin 10.0 Gm., hematocrit 31, red blood count 2.91 million, white blood count 14,950 with slight shift to the left. Urinalysis showed protein 2 plus; negative for sugar and acetone; red blood cells too numerous to count; 4 to 6 white blood cells per high-power field, many bacteria and epithelial cells. Blood chemistry determinations showed blood urea nitrogen 58, carbon-dioxide combining power 39.0 vol. per cent or 17.4 meq., and chlorides 573 vol. per cent or 97.4 meq. Cultures of the uterus and blood were taken on admission.

The patient was given tetracycline intravenously and supportive therapy. Her temperature remained between 101 and 104° F. and she grew worse steadily with increasing jaundice and enlargement of the liver. The hemoglobin dropped to 7.3 Gm., in spite of multiple small transfusions. It was noted that the urine was a dark brown color. On

January 23 in spite of therapy, the patient became semicomatose and her temperature rose to 105.4° F. By this time, the uterine cultures had returned and proved to be pure cultures of *Clostridium perfringens.*

The tetracycline was stopped and 40,000 units of perfringens antitoxin was given intravenously. This was repeated three times during the next twenty-four hours. Later that day 1,000,000 units of penicillin was given and repeated every three hours. Within the twenty-four hours, her temperature was down to 100° F. and she appeared lucid and objectively much better. On January 24 she received the same medication but the antitoxin was given only twice the third day and then once daily for two additional days. She became afebrile during this time. Repeated cervical cultures on Jan. 23, 1954, showed a mixed culture of *Clostridium perfringens* and *Bacillus coli.* Repeated blood cultures were sterile. She remained afebrile until February 7.

At this time she developed afternoon elevations of temperature ranging from 100 to 102.6° F. These occurred for four days and during this time a tender cystic mass appeared in the location of the right tube and ovary. She again was fine until February 11, when she suddenly developed severe abdominal pain, with fever ranging from 102 to 104° F. Physical examination disclosed decreased peristalsis and signs of generalized peritonitis. On examination there were bilateral tuboovarian masses. She was again placed on penicillin. Menses began February 16. By February 22 she was afebrile, although a 4 to 5 cm. tuboovarian mass remained on the right side and marked induration on the left side. Findings were essentially unchanged at the time of follow-up two months later.

Comment

Clostridium perfringens is frequently found as an inhabitant of the normal reproductive tract, and it is only when there is associated trauma or necrotic tissue present that the perfringens bacillus becomes pathogenic. These conditions are usually fulfilled in a case of induced septic abortion. In these cases the infection is frequently restricted to the uterine cavity. The marked systemic reaction which these patients manifest is due to the absorption of the toxins manufactured by the bacillus. Alpha toxin, which has been identified as lecithinase C is the most potent toxin produced. It is responsible for the intravascular hemolysis with the resulting rapid anemia and icterus. It can also produce hemorrhage as a result of its necrotizing action on capillary and arteriolar walls.

Adequate treatment consists of neutralizing the toxins and killing the bacteria. Perfringens antitoxin is specific for neutralization of the toxin and penicillin inactivates the bacillus itself.

Our patient received 480,000 units of antitoxin during a five-day period, 320,000 units of which was given during the first forty-eight hours. In addition, one million units of penicillin was given every three hours. The response to this therapy was dramatic. She became lucid within twenty-four hours after having been semicomatose for forty-eight hours. The initial rapid improvement on this therapy is most likely due to a neutralization of the toxins circulating in the blood stream. In addition to this therapy, the patient should have blood transfusions, if she is anemic, and fluids to re-establish the electrolyte balance if this is necessary.

It is our opinion that there should be no instrumental interference in the management of these cases. The therapy should be directed toward controlling the infection and surgery resorted to only in the event of life-threatening hemorrhage.

Specific therapy is frequently delayed twenty-four to forty-eight hours until the bacteriology report is available. This was a factor in our case; but if the clinician suspects the possibility of a perfringens infection, a positive bacteriology report may be obtained in twelve hours after incubation with both aerobic and anerobic plates.

Summary

A case of *Clostridium welchii* infection following abortion, treated with large doses of antitoxin and penicillin, has been reported.

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EVALUATION OF Rh HAPTEN

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IN 1947 there appeared the first report[2] on a fraction of human red blood cells which inhibits the agglutinating properties of anti-Rh serum. This fraction was described in detail in 1949[3] under the name of Rh hapten, although acknowledged to be in crude form. It has been demonstrated more recently[4] that this substance will adsorb antibody from anti-Rh serum and that the adsorbed antibody nitrogen can be determined quantitatively on the fraction particles. Barnard[1] has confirmed the observation that the fraction appears to be "hapten in the Landsteiner sense." A hapten is a substance which, when combined with a suitable carrier, can stimulate antibody production in a host and can alone react specifically with that antibody, but which with no carrier cannot by itself produce antibodies.

Since 1947 we have used this fraction therapeutically in 135 cases of sensitized Rh-negative women. We wish to report briefly the current simplified production methods, the results obtained in treated cases, with a few case histories, and to point out two areas in which we believe the Rh hapten may be useful in the future.

Preparation of the fraction is accomplished by pooling the cells from 6 pints of outdated Rh (D) positive bank blood of any group. Two volumes of 95 per cent ethyl alcohol are added slowly to this pool in a 4 gallon wide-mouth bottle and the whole is stirred thoroughly. The precipitated blood in alcohol is allowed to stand overnight at room temperature. The next day the precipitate is separated by filtration with suction and to this is added 2 volumes (exactness of measurement is not critical) of dichloromethane. The precipitate is allowed to remain in the dichloromethane for at least six hours or as long as is convenient, with intermittent, thorough shaking. Then the solvent is separated from the precipitate by suction filtration and this liquid is distilled off or evaporated under a hood with an electric fan. The residue is the active material in crude form, which may be weighed, dissolved in warm 95 per cent alcohol, and dispensed in 2 ml. ampules at concentrations of 100 to 200 mg. per milliliter of alcohol.

The fraction is administered as follows: draw 6 ml. sterile normal saline into a 10 ml. syringe. Then draw into the syringe the contents of one ampule (200 to 400 mg.) and mix by rotation to produce a milky fluid. The whole is injected slowly into the gluteal muscles, with the use of a 2 inch, 20 gauge needle. Experiments have been made with administration of the fraction orally in the form of pills made with powdered lactose, but this work is not

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complete. For administration to babies, one ampule of the Rh hapten is drawn into 25 to 30 ml. sterile normal saline and the whole is given slowly by injection into the muscles of the back.

The five case histories which follow are representative of the type of results which can be achieved and illustrate the use of the hapten. Cases in which work was begun before pregnancy was initiated (a procedure which we strongly recommend) are reserved for a later report.

CASE 1.—Mrs. J. D. had four living and well children, all Rh positive (R1r). On Aug. 12, 1945, at St. Mary's Hospital in Rochester, New York, she was delivered of a 6 pound, 10 ounce female infant that showed icterus and an enlarged abdomen at birth and died in 25 minutes. Records give the anatomic diagnosis as "erythroblastosis fetalis, with icterus, hepatomegaly, splenomegaly and characteristic placental changes." The spleen weighed 90 grams, the liver 200 grams. The sixth child, a male, 6 pounds, 15 ounces, was born on Sept. 10, 1946, St. Francis Hospital, Pittsburgh. This child died two hours later and autopsy showed "slight icterus, hepatomegaly, splenomegaly and generalized anasarca; erythroblastosis fetalis." The red blood count at birth was 3.4 million, the spleen weighed 40 grams, the liver 180 grams. Child 7 was a female, 7 pounds, 5 ounces, born on March 12, 1948, at Butler County Memorial Hospital, near Pittsburgh. The child was stillborn but not macerated, and showed "generalized icterus of a mild degree, severe, generalized cyanosis, abdomen distended and liver palpable as far down as the pelvis. . . . The abdominal viscera are displaced downward by the enormous dark tan to purple liver." Histology showed "erythropoietic islands in all organs. . . . Diagnosis: erythroblastosis fetalis; hydrops fetalis."

For child 8, Mrs. J. D. was treated with Rh hapten, beginning the third month, when her initial Rh antibody titer in plasma was 10 units, receiving a total of 20.8 Gm. Child 8 was born Jan. 26, 1950, weighing 8 pounds, 8 ounces, at West Penn Hospital. The baby was Group B, R1r, with a doubtful Coombs test and bilirubin 4.8 mg. on cord blood and a red blood count of 5.7 million. The hemoglobin was 17 gm. On January 30 the red blood count was 5.5 million and hemoglobin 17 Gm. On February 2 the red blood count was 5.6 million and hemoglobin 17.5 Gm. At six weeks the red blood count was 5.0 million. The child was not treated in any way, was discharged on Feb. 3, 1950, and has progressed normally. The mother is Group B, rr; the father Group O R1.

CASE 2.—Mrs. B. B. had one living child, then lost 4 infants in succession, each of which either died shortly after birth or was stillborn. Child 6 was born March 31, 1937, at Allegheny General Hospital, Pittsburgh, a male weighing 9 pounds, 3 ounces, that survived for one-half hour. Records show "congenital dropsy and erythroblastosis fetalis. . . . The cause of death was pulmonary atelectasis and hemorrhage, acute dilatation of the right side of the heart and a massive intra-abdominal hemorrhage. Due to edema, petechial hemorrhages, large liver and spleen, hyperplasia of the bone marrow, this was a case of congenital dropsy due to erythroblastosis foetalis. This was a typical case of extramedullary hemopoiesis . . . in the lungs, spleen, liver, adrenals, kidneys and testes."

Child 7 was a female, no weight given, born Aug. 15, 1940, at Allegheny General Hospital. The infant died almost at once; the autopsy report reads: "erythroblastosis of heart muscles and lung, tumor-like extramedullary hemopoiesis of liver and spleen, all of the hemopoietic elements of the bone marrow showed extreme hyperplasia. The above findings, added to the presence of generalized edema and large numbers of nucleated red cells in the vessels of all of the other organs, presented a typical erythroblastosis foetalis."

For child 8, Mrs. B. B. was treated, starting at the second month, when the Rh antibody titer was 10 units, and received a total of 15.8 Gm. Rh hapten. Child 8 was born Feb. 6, 1950, a male weighing 7 pounds, 5 ounces, at West Penn Hospital. The baby was Group A, R1r; the cord blood showed a positive Coombs test, red blood count 5.5 million, hemoglobin 18 Gm. The smear had 5 erythroblasts per 100 white blood cells; the bilirubin 4.5 mg. On February 8, the red blood count was 5.6 million, hemoglobin 18 Gm.; on February 11, the red blood count was 5.3 million, hemoglobin 17 Gm.; on February 15 the red blood

count was 5.1 million, hemoglobin 16 Gm. The baby was discharged on Feb. 15, 1950, with no treatment; progress has been normal. On March 20, 1950, the red blood count was 5.1 million, hemoglobin 16 Gm. The mother is Group A, rr; the father is Group A, R1.

CASE 3.—Mrs. M. M. had one normal child, Group A, R1r. On Sept. 17, 1938, she was delivered at West Penn Hospital of a male child, weight unrecorded. The chart states: "died several hours after birth—thick mucus in trachea and bronchi. Asphyxiation." This was a full-term birth; no autopsy was done. Child 3 was born Sept. 7, 1941, at West Penn Hospital, a male weighing 7 pounds, 8 ounces. This was a full-term stillborn infant estimated to have been dead about a month. Studies were made on the placenta: "Some of the placental villi show an increased cellularity by mesenchymal cells. In addition, many nucleated red cells are seen." The autopsy showed: "1) macerated, normally formed fetus; 2) post mortem autolysis of all organs; 3) hydrothorax; 4) ascites; 5) pulmonary atelectasis, complete." The spleen weighed 8 grams, the liver 210 grams. Child 4 was an 8 pound male, born March 13, 1951, at West Penn Hospital. The mother began treatment at the third month, when the antibody titer was 5 units, and received 21 Gm. Rh hapten during pregnancy. The baby was Group A, R1r, with a positive Coombs test, bilirubin 7.5 mg., red blood count 4.9 million, hemoglobin 14.5 Gm. on cord blood. On March 15 the red blood count was 4.9 million, hemoglobin 14.5; on March 18 the red blood count was 4.8 million, hemoglobin 13 Gm. The baby received 1,200 mg. Rh hapten, but no transfusions. He was discharged with the mother on March 19, 1951, and has progressed normally.

Child 5, a 7 pound, 10 ounce male, was born May 24, 1954, at West Penn Hospital. The mother was treated again, starting at the second month when the Rh antibody titer was 10 units, and received 72 Gm. Rh hapten during pregnancy. The child was Group A, R1r, with a positive Coombs test, red blood count 4.6 million, hemoglobin 15 Gm. on cord blood. On May 28 the red blood count was 4.4 million, hemoglobin 14 Gm.; on June 2 the red blood count was 4.0 million, hemoglobin 12.5 Gm. The baby received 200 mg. Rh hapten at birth, but no transfusions. Mild jaundice was noted on May 25, but had disappeared by May 31. He was discharged on June 4, 1954. He has been completely normal; on Nov. 12, 1954, the red blood count was 5.1 million. The mother is Group A, rr; the father is Group A, R1R2.

CASE 4.—Mrs. M. Mi. received three blood transfusions in 1945. Donors for the three transfusions were available in 1952 and were tested. Mrs. Mi is Group A, rr. One donor was also Group A, rr. The other two were Group A, R1. Mrs. Mi does not recall any reactions to the transfusions. In 1950, Mrs. Mi had one normal girl, who is Group B, R1r. The father is Group B, R1. Child 2, a 7 pound, 2 ounce male, was born April 20, 1952, at West Penn Hospital. The mother was treated, starting with the second month when her Rh antibody titer was 10 units, and received a total of 26.5 Gm. Rh hapten. The baby was Group AB, R1r, with a positive Coombs test, a red blood count of 5.1 million, and 16 Gm. hemoglobin. The red blood cell and hemoglobin levels did not waver during the first week of life and the baby was discharged with the mother and has progressed normally.

CASE 5.—Mrs. S. K. was delivered of her first child, a 7 month, stillborn male on July 7, 1944, at Rochester (Pa.) General Hospital. This child was anencephalic. Child 2 was the product of a 7 months' gestation, a 4 pound male, born March 18, 1946, at the same hospital, where pertinent records read: "upper half of lung poorly aerated, baby became cyanotic at intervals." The infant was discharged on May 2, 1946, weighing 5 pounds, 2 ounces; he is Group B, R1r, and at the age of 3 cannot sit up, walk, or perform any functions unaided. No Rh studies were made at birth. Child 3, a 6 pound, 5 ounce male, was born at term on Oct. 13, 1949, at West Penn Hospital. From the third month on, the mother had been treated, when it was discovered that her Rh antibody titer was 160 units. She received a total of 5 Gm. hapten. The baby was Group B, R1r, with negative Coombs test, a red blood count of 5.0 million, hemoglobin 16 Gm., 1 erythroblast per 100 white blood cells. On October 15 the red blood count was 5.1 million, hemoglobin 16 Gm.;

on October 17 the red blood count was 5.0, hemoglobin 15 Gm.; on October 18 the red blood count was 5.4, hemoglobin 16.5 Gm. The child received 600 mg. Rh hapten in 3 doses of 200 mg. each. He was discharged with his mother and progressed normally.

Child 4, a male, 7 pounds, 2 ounces, was born Aug. 13, 1953, at West Penn Hospital. The mother was treated, beginning at the second month when the Rh antibody titer was 80 units, and receiving 42 Gm. during the pregnancy. The baby was Group O, R1r, with a positive Coombs test, red blood count 4.5 million, hemoglobin 13 Gm., 39 erythroblasts per 100 white blood cells. On August 15, the red blood count was 4.2 million, hemoglobin 13 Gm.; on August 17 the red blood count was 4.4 million and hemoglobin 12.5 Gm.; on August 18 the red blood count was 4.3 million, hemoglobin 13.5 Gm.; on August 20, the red blood count was 4.4 million, hemoglobin 14 Gm. The baby received 200 mg. Rh hapten daily during his stay in the hospital, but was given no transfusions. There was perceptible jaundice on the third day, which cleared on the tenth day of life. The baby has developed normally.

Comment

Results with 135 cases show that 53 per cent of these women who previously had lost erythroblastotic babies had normal infants after treatment with Rh hapten during pregnancy. There were no cases of demonstrable kernicterus. In the series *no baby was lost in a single case if treatment was begun before a new pregnancy was initiated and continued with daily injections from as soon as pregnancy was suspected until term.** Early inductions are not recommended in any of these treated cases.

Experience has led us to believe that if the fraction is given to a woman when she first becomes sensitized to Rh, before she has lost an infant, it may be possible to avoid erythroblastosis not only in that pregnancy, but in any pregnancy, provided treatment is given with each one. Salvage of infants from mothers with no history of previous erythroblastotic losses is better than 98 per cent. This aspect of the use of Rh hapten needs further exploration.

With women who have lost one or more infants because of erythroblastosis, it seems to us desirable to begin treatment before a new pregnancy is established. The woman may be given one or two injections weekly of 200 to 400 mg. each for from three to four months or until her Rh antibody titer has disappeared. She may then be advised to become pregnant and as soon as she suspects pregnancy she should receive from 200 to 400 mg. daily until term. Other than local discomfort, we have never seen a reaction to these injections. We strongly advise against early induction of labor unless reasons other than Rh sensitization make this imperative. With patients under treatment, there is no advantage (and obvious disadvantage) to inducing labor early with the resulting premature infant and the concomitant hazards. It is important to emphasize the fact that not one child has been lost to sensitized women whose treatment began before a new pregnancy was initiated and was continued throughout pregnancy as first specified.

At delivery the doctor may determine by the customary criteria if the infant requires an exchange transfusion. In a large proportion of cases this will not be necessary. From 1947 to 1952 at Western Pennsylvania Hospital,

*Since this writing, one infant has been lost by a mother who was treated before as well as during pregnancy. In this case there was an interval of several months between prior treatment and that during pregnancy, an unusual and not propitious circumstance.

the Rh hapten was used exclusively for newborn infants with no transfusions employed. There is no reason, however, why we should not avail ourselves of all means at our disposal. We feel that if the Rh hapten is used properly fetal deaths due to Rh incompatibilities can be eliminated. It seems likely that with intelligent use of Rh hapten plus exchange transfusion, we can cross off erythroblastosis fetalis as a cause of fetal and neonatal mortality.

Summary

In this paper, we have detailed the current methods of Rh hapten production and have described its administration to the sensitized Rh-negative woman. Five representative case histories have been presented along with results obtained in the first 135 cases treated. Recommendations have been made as to the most effective use of the Rh hapten with suggestions as to further investigation.

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NONPUERPERAL INVERSION OF THE UTERUS

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NONPUERPERAL inversion of the uterus is rare. The purpose of this paper is to present another case with spontaneous reduction after excision of protruding myomas.

Case Report

Mrs. E. R., aged 55 years, gravida iii, para i (at age 31), abortion ii, was admitted to the District of Columbia General Hospital on Oct. 23, 1954. Irregular genital bleeding had been noted for fifteen years following the menopause. For four years she had noted recurrent prolapse of a mass through the vagina whenever she coughed, sneezed, or strained strenuously. On each occasion she was able to reduce the mass manually. Two days prior to admission while straining at stool she felt a "sickening feeling" in the lower abdomen and again a mass prolapsed through the vagina which she was unable to replace. After two days in bed she consulted a physician and was referred to the hospital.

Examination on admission showed a thin, gray-haired white woman, confused, apprehensive, pale, moderately dehydrated, and poorly nourished. The oral temperature was 100° F., pulse 88, blood pressure 150/85. The abdomen was scaphoid with no palpable masses. Laboratory studies were normal except for a moderate anemia. There was a foul-smelling, necrotic mass protruding about 10 cm. from the vagina. This was found to be a completely inverted uterus with two blackened necrotic submucous myomas 6 to 8 cm. in diameter attached to the inverted fundus by pedicles 3 to 4 cm. in diameter. The upper third of the vagina protruded to the introitus but the lower two thirds of the vagina and the urethra were well supported. The bladder herniated into the anterior segment of the vaginal protrusion but the patient was continent. The uterus and adnexa could not be felt on rectal examination which disclosed a finger-tip depression of the anterior wall on the posterior rim of the inversion funnel. A chest x-ray was normal. An intravenous pyelogram showed contraction and distortion of the bladder.

The management of the patient consisted of an immediate Sitz bath, the insertion of a Foley catheter, local hydrogen peroxide compresses followed by a sulfonamide cream and systemic antibiotics. About 48 hours after admission the two necrotic myomas were excised after clamps had been applied to each pedicle. The clamps were removed 48 hours later without bleeding. The inverted uterus was reduced into the vagina and a brief unsuccessful attempt was made to reduce the inversion. Hysterectomy was anticipated but this was deferred in order to improve the patient's nutritional status and to allow the edema and infection to subside. Five days after removal of the clamps examination showed a clean, closed cervix with the uterus reinverted and normal in position and size. The patient was discharged on the fourteenth hospital day.

The pathological report on the two excised tumors was leiomyoma showing hemorrhagic infarction.

Comment

Nonpuerperal or gynecological inversion must be distinguished from the more common puerperal or obstetrical inversion. Puerperal inversion has been arbitrarily defined as *acute* if it occurs within 30 days of the termination of pregnancy and *chronic* after 30 days.

All cases of nonpuerperal inversion should be regarded as chronic. There is little definitive value in the terms "acute," "gradual," and "sudden" which have been used. There is some merit in following Jones'[1] classification of: (a) tumor produced and (b) idiopathic. The latter are very rare; only one case has been reported in the last forty years.[2] Almost all nonpuerperal inversion of the uterus is associated with either benign or malignant tumors.

The degree of inversion permits a practical clinical classification into: (a) *incomplete* inversion of uterus, (b) *complete* inversion of uterus, (c) complete inversion of uterus and vagina. Unless the fundus has extruded through the external os, inversion is incomplete. If any part of the fundus is through the external os then it is complete inversion. In Das'[3] extensive review of inversion of the uterus he was able to collect 58 cases of the nonpuerperal type. Of 53 cases which he was able to classify, 2 were incomplete, 49 were complete, and 2 showed complete inversion of both uterus and vagina. All complete inversion of the uterus may have an associated partial inversion of the upper vagina.

Fig. 1.—Inversion of the uterus with two necrotic fibromyomas.

Etiology.—With rare exceptions nonpuerperal inversion of uterus follows the development of an intrauterine tumor. In Das' review of 54 cases, 47 presented fibroids, 4 sarcoma, and 3 endometrial carcinoma. The fibroids are usually submucous, either sessile or with a short, thick pedicle.

Mechanism of Inversion.—The tumor distends the uterus and may dilate the cervix. The uterine wall is particularly thin, weak, and paralyzed at the base of the tumor pedicle. The surrounding myometrium is excited with resultant expulsive contractions. The more active myometrium expels both the tumor and the paralyzed portion of the myometrium. The weight of the tumor in itself may be a factor. Manual traction on a protruding tumor may assist in producing the inversion. Complete inversion may be facilitated by straining or coughing. It is probable that any wasting disease, in our own patient malnutrition, predisposes to inversion of uterus.

Symptoms.—Some chronic genital discharge which may be menorrhagia, metrorrhagia, or leukorrhea is usually seen in nonpuerperal inversion of uterus. It is rare to have an acute hemorrhage with shock except in the occasional case of the idiopathic variety.[2] The chronic blood loss usually produces anemia with associated fatigue and weakness. Patients commonly complain of some pelvic discomfort, in walking, standing, or sitting. There is an awareness of a tumor in the vagina, a "bearing down" sensation, or there may be bladder irritability with frequency and dysuria. With necrosis and infection the patient may be generally ill with malaise and anorexia.

The diagnosis of nonpuerperal inversion of the uterus can readily be made if the entity is considered. In many of the cases reported the inversion was not recognized until operation. Aborting myoma is the most common misdiagnosis.

Diagnostic Signs.—With inversion of the uterus the cervical ring may or may not be recognized, but it is impossible to find the os or to probe the endometrial cavity. Rectoabdominal examination shows an absence of the uterus in the pelvis or a cup-shaped inversion funnel. The degree of vaginal inversion is easily determined by digital palpation. The absence of a previously noted tumor is a significant sign.

Treatment.—No gynecologist acquires much experience in treatment of nonpuerperal inversion of the uterus since it is so rare. Most nonpuerperal inversions are chronic and are associated with an intrauterine tumor. If the tumor is malignant, treatment of the inversion is incidental to the cancer therapy.

If the tumor is a myoma, then the most conservative procedure to achieve a cure is indicated. Das[3] reported 13 cases manually replaced after excision of tumors. Even with failure to reinvert the uterus on the initial attempt, a delay of several days is justified. Much of the infection and edema will subside and the uterus may be reduced spontaneously as in 3 cases in Das'[3] review and our own case.

Summary

A case of spontaneous reinversion of the uterus after vaginal myomectomies has been presented. The subject of nonpuerperal inversion of the uterus has been reviewed. Emphasis has been given to making the preoperative diagnosis and the advantages of delay in hysterectomy if vaginal myomectomy is feasible.

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UTERUS DIDELPHYS WITH DOUBLE PREGNANCY*

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THIS case report is concerned only with the true uterus didelphys in which lack of fusion of the Müllerian system has resulted in the development of a double uterus, each with its separate cervix and vaginal tract. Simultaneous pregnancy in each cavity of a true uterus didelphys has been considered to be a very rare occurrence, and an extensive review of the literature disclosed only three authenticated cases in which such pregnancies resulted in the delivery of two viable infants. To our knowledge, however, three such patients delivered viable infants in the year 1954 alone which leads us to believe that this condition is not as rare as was formerly thought.

Every case of uterus didelphys terminating in the delivery of two viable infants should be reported so that a definite policy for management can be formulated. Current obstetrical texts acknowledge the possibility of occurrence of the condition but fail to offer any helpful advice as to the course of labor and the method of choice for delivery. According to older case reports, delivery was effected by cesarean section and a canvass of a number of the obstetricians around this large medical center showed that the majority believed that a section delivery was advisable. In 1954 Brody reported upon a patient who went into spontaneous labor and delivered a living infant following which he immediately induced labor in the second uterus by Pitocin and amniotomy. In the same year and without knowledge of Brody's successful case we elected to deliver vaginally our patient whose course is reported in detail below. Following the widespread dissemination of the news of our successful delivery by the lay press an obstetrician in another institution wrote to say that on the basis of our successful outcome he was managing a similar case in a like manner and having delivered the first infant uneventfully was awaiting the spontaneous onset of labor with the second. Thus it appears that when the obstetrician is faced with the problem of a double pregnancy occurring in each side of a uterus didelphys the accoucheur can anticipate uneventful labor and delivery, probably at widely separated dates, of each fetus. Only the compilation of more case reports can prove or disprove this thesis.

Mrs. T. C., a 32-year-old white housewife, was first seen at the prenatal clinic of the U.S. Naval Hospital, Chelsea, Massachusetts, on Oct. 28, 1953. Her complaint was vaginal

*The opinions contained herein are those of the authors and do not reflect the policy of the Department of Defense.

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bleeding of a scanty nature for the past three days, morning nausea, and frequency of urination. The last menstrual period had been on July 26, normal in nature. She had one previous pregnancy resulting in premature labor and delivery at the thirty-second week of gestation. The infant weighed 3 pounds, 9 ounces, and died on the seventh neonatal day of prematurity. At the time of this delivery the doctor divided a vaginal septum but apparently did not suspect the presence of a second cervix or uterus. Following parturition the breasts became engorged and lactated.

Fig. 1.—X-ray of abdomen at fifth month of gestation, showing twin pregnancy.

General physical examination on October 28 was essentially normal. On pelvic examination two cervices could be visualized; both appeared typical of early intrauterine gestation. Several remaining tags of the divided vaginal septum were identified. Two uteri were palpable lying one to the left and one to the right. Each corpus was softened and enlarged to the size of a ten weeks' gestation. The bony pelvis was average gynecoid and was deemed favorable for vaginal delivery. A tentative diagnosis of a double pregnancy in a uterus didelphys was made. X-rays taken in the fifth month of gestation confirmed the presence of a twin pregnancy (Fig. 1).

The prenatal course proceeded uneventfully with both uteri continuing to enlarge equally and symmetrically. The right fetus lay in a frank breech position, the left in a vertex presentation.

On March 15, 1954, at approximately the thirty-first week of gestation, the right uterus went into labor following spontaneous rupture of the membranes. As expectant treatment had been decided upon, 1,000 c.c. of whole blood was cross-matched and the patient observed closely. The fetus engaged as a frank breech and after two hours and forty-nine minutes

Fig. 2.—X-ray of abdomen following delivery from right uterus.

A. *B.*

Fig. 3.—*A*, Hysterosalpingogram showing right uterine cavity and tube taken eight weeks post partum with cannula in left uterine cavity.
B, Hysterosalpingogram after injection of dye in left uterine cavity.

was delivered by breech assistance under 2 mg. Pontocaine saddle block anesthesia following the technique described by Dorgan and associates[4] with mediolateral episiotomy. The infant was a living female who weighed 3 pounds, 14 ounces, normal except for prematurity. She breathed and cried spontaneously. The placenta was delivered intact in three minutes with a blood loss estimated at a total of 200 c.c.

During the course of labor in the right uterus the left uterus displayed a moderate increase in tone and became quite irritable but did not exhibit any regular contractions. Following delivery of the first fetus mild irregular contractions appeared in the left uterus and persisted for about six hours, diminishing in intensity and completely disappearing after that time. There was no effacement or dilatation of the cervix on that side.

Penicillin was administered prophylactically for five days post partum for fear that labor might return during this period of maximal bacterial growth in the parturient genital tract. Following this first delivery there was no evidence of breast engorgement or lactation in either breast although no measures were instituted to suppress it. The left uterus gradually assumed a mid-abdominal lie during the next three days (Fig. 2).

The patient was discharged home on the ninth postpartum day to be followed in the prenatal clinic and to await the spontaneous onset of labor in the left uterus. She was seen at weekly intervals at which time the delivered uterus was noted to be involuting normally and was found to be assuming a position posterior and to the right of the pregnant uterus. The latter continued to enlarge at a normal rate.

On April 5, 1954, at approximately thirty-four weeks of gestation, the left uterus went into labor following spontaneous rupture of the membranes and after two hours and four minutes of normal labor with the fetus in right occiput transverse position a living male infant was delivered. Low forceps delivery was accomplished with a medilateral episiotomy under Pontocaine saddle block anesthesia. The infant weighed 4 pounds, 6½ ounces, and was normal except for prematurity. Respiration and cry were spontaneous. The placenta was delivered intact after three minutes; the total blood loss estimated at 350 c.c. The breasts became engorged on the third day following this delivery and lactation was suppressed by the administration of Vallestril.* The puerperium was uneventful and the patient was discharged on the seventh postpartum day.

At subsequent visits both babies and the mother have been well. Menses were reestablished at six weeks and were normal. A study of the upper urinary tract for detection of one of the congenital abnormalities so often associated with anomalies of the Müllerian system showed both kidneys and ureters to be normal. A salpingogram with a contrast medium showed the typical picture of uterus didelphys (Fig. 3).

Summary and Conclusions

1. Simultaneous pregnancy in each side of a uterus didelphys is probably not as rare an occurrence as was formerly believed.

2. Until a definite policy for management of such cases has been formulated each such obstetrical delivery should be reported.

3. A case of double pregnancy in a uterus didelphys treated expectantly is presented. It appears that such cases can be successfully managed by awaiting the spontaneous onset of labor in each uterus, and dealing with each delivery as if it were a separate single pregnancy.

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*3-(6-methoxy-2-naphthyl)-2, 2-dimethyl pentanoic acid.

AN UNUSUAL COMPLICATION OF CULDOSCOPY

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CULDOSCOPY is often a very valuable diagnostic aid and its use is undoubtedly increasing. There are complications reported both during and after culdoscopy, however.

Those occurring after culdoscopy have mainly arisen from two sources:

1. Air escaping from around the culdoscope into the extraperitoneal space and thence to the mesentery of the sigmoid,[5] to the retroperitoneal spaces and upward to mediastinal and cervical regions,[7] or even to the subcutaneous tissue of the upper part of the trunk.[1, 9]

2. Bleeding from the edge of the wound with formation of a mass in the posterior fornix containing blood.[2, 8]

The following is the report of an additional complication:

M. K., a 27-year-old white woman, was admitted on April 2, 1954. She was gravida iv, para i, with a history of one abortion and one tubal pregnancy. She stated that her last normal period had been Feb. 20, 1954. About March 20 she had scanty vaginal bleeding for two days. On March 26 she began to experience right lower quadrant pain which steadily increased in severity. She noted some urinary frequency but no dysuria. She further recounted that she had had an appendectomy in 1950, a left salpingectomy for a tubal pregnancy in 1952, and a left oophorectomy in 1953.

Physical examination showed some colostrum present in the breasts and bilateral lower quadrant tenderness with rebound tenderness on the right side. Pelvic examination showed the uterus to be anteflexed, anteverted, and tender to palpation; there was tenderness of the adnexa on the left and on the right a 4 to 5 cm. cystic mass which was fixed and very tender.

A provisional diagnosis of right tubal pregnancy was made and culdoscopy was performed. The right ovary was visualized and found to be enlarged and cystic. The right tube could not be seen but, since no blood was present in the peritoneal cavity or close to the right ovary, it was felt that ectopic pregnancy had been ruled out.

The following day, when old records were available, it was discovered that she had previously been subjected to culdoscopy in 1952 for a possible ectopic pregnancy but that salpingitis was found. Subsequently that year she had a Falk procedure* and then in 1953 at another hospital she had had a left salpingo-oophorectomy.

The patient continued to complain of lower abdominal pain and on April 5 a pelvic examination disclosed a mass prolapsed through the small culdoscopy site. In the operating room the culdoscopy site was enlarged by means of a colpotomy incision exposing the lower part of the pelvis for examination. The sigmoid colon was visualized and the prolapsed mass proved to be two appendices epiploicae of the sigmoid colon. These were ligated at the bases, excised, and the bowel replaced. The colpotomy incision was closed with interrupted sutures. The postoperative course was uneventful.

*By "Falk procedure" is meant bilateral cornual resection of the Fallopian tubes without salpingectomy. This procedure has been advocated in certain cases of chronic recurrent gonorrheal salpingitis as an alternative to the more radical procedures such as bilateral salpingectomy or bilateral salpingectomy with supracervical or total hysterectomy.

Comment

Culdoscopy has been done several hundred times in the department[8] and this was the first instance of prolapse of any intraperitoneal tissue. Several patients have had culdoscopy more than once and Decker[4] feels that previous culdoscopy is not in itself a contraindication to the procedure. This might have been a factor in delayed approximation of the edges of the foramen, however.

At the end of the procedure as outlined by Eichner,[6] pressure is applied firmly on the upper abdomen as the patient slowly slips into the prone position and is maintained for thirty to sixty seconds before the sleeve is removed. Again it was suggested that this increase in intraperitoneal pressure might have initiated the prolapse.

Commonly some distention, upper abdominal discomfort, and shoulder pain for twenty-four to thirty-six hours are seen, but the persistence of pain should certainly suggest the possibility of a complication.

Summary

A case has been presented of prolapse of two appendices epiploicae in a patient following her second culdoscopic examination.

Grateful acknowledgment is made to Dr. Newlin F. Paxson, Chief of the Division of Women, and to Dr. Bruce V. MacFadyen, Professor of Gynecology, for their permission to use this case and their encouragement in reporting it.

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CARCINOMA OF THE FUNDUS OCCURRING IN DOUBLE UTERUS

Report of Three Cases

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CONGENITAL malformations of the female genitals occur as a result of failure of fusion or resorption of the Müllerian duct system during the early months of fetal life. These anomalies are most often observed in the form of duplication, in some degree, of the uterus and cervix or vagina. The coexistence of this type of abnormality with carcinoma of the body of the uterus has been reported infrequently.

TABLE I. REPORTED CASES IN WHICH CARCINOMA OF THE UTERINE FUNDUS WAS ASSOCIATED WITH CONGENITAL UTERINE ABNORMALITIES

NO.	REPORTED BY*	YEAR REPORTED	CLASS OF ABNORMALITY	TYPE OF MALIGNANCY
1	Hofmeier	1902	Uterus duplex	Adenocarcinoma
2	Mintrop	1912	Uterus bicornis	Adenocarcinoma
3	Unterberger	1913	Uterus duplex unicollis	?
4	Beck		Uterus bicornis	Adenocarcinoma
5	Peterson	1923	Uterus bicornis unicollis	Malignant adenoma
6	Norris and Vogt	1924	Uterus bicornis	Adenocarcinoma
7	Brandes	1925	Uterus duplex	Adenocarcinoma
8	Brandes	1925	Uterus bicornis duplex	Squamous-cell carcinoma
9	von Franqué	1926	Uterus bicornis subseptus	Adenocarcinoma
10	Thiers[2]	1934	Uterus bicornis	Adenocarcinoma
11	Motta[3]	1934	Uterus bicornis	Adenocarcinoma
12	Danesi[4]	1935	Uterus didelphys	Chorionepithelioma
13	Case records of Massachusetts General Hospital[5]	1937	Uterus septus	Adenocarcinoma
14	Shelley[6]	1938	Uterus biseptus	Adenocarcinoma
15	Corbet[7]	1949	Uterus bicornis	Adenocarcinoma
16	Siegler[8]	1950	Uterus didelphys	Adenocarcinoma
17	Zippis[9]	1953	Uterus duplex	Adenocarcinoma

*The first nine cases are taken from von Franqué.[1]

*The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Von Franqué,[1] in reviewing the literature from 1777 to 1930, found reports of 9 cases in which malignant disease of the fundus occurred in a malformed uterus. In the ensuing twenty-four years, an additional 8 cases have been recorded.[2-9] A complete list of these 17 cases is presented in Table I. The following reports of 3 cases bring the total number reported to 20.

Report of Cases

CASE 1.—A 49-year-old full-blooded Indian woman presented herself at the Mayo Clinic in 1949 complaining chiefly of a brownish-yellow vaginal discharge of six months' duration. This had been treated elsewhere by the injection of estrogen compounds. The menses had been normal and regular prior to the onset of the condition at hand.

This patient had been seen previously at the clinic on several occasions for general examinations. At the time of her first visit in 1919, a surgical diagnosis of tuberculosis of the axillary glands had been made.

Two surgical procedures had been performed elsewhere: bilateral salpingectomy and appendectomy in 1925, and cholecystectomy for stones in 1948. Eight months prior to her admission in 1949 she had been found to be diabetic, and the diabetes was being controlled with difficulty by diet and the use of insulin.

She had been pregnant three times, with normal delivery in each case. Only one child had survived infancy, however.

This patient was obese, weighing 200 pounds, but she apparently was in good health. The systolic blood pressure was 120 and diastolic 80, in millimeters of mercury. The uterus was three times normal size and was freely movable. Fibroid tumors of the uterus had been reported in an examination in 1939. The adnexal areas were normal. The cervix was eroded, and a brownish-yellow discharge was seen. Otherwise, results of examination were negative.

Glycosuria of Grade 4 was recorded. The value for fasting blood sugar was 327 mg. per 100 c.c. of blood. The content of hemoglobin was 11.3 Gm. per 100 c.c. of blood, and the results of serologic tests were negative. Roentgenograms of the thorax were interpreted as showing nothing abnormal.

A clinical diagnosis of fibromyoma of the uterus was made on the basis of the pelvic observations, and total abdominal hysterectomy was advised and accepted.

Operation was performed. The uterus was found to be adherent against the anterior abdominal wall, apparently as a result of a previous suspension. Exploration of the right part of the abdomen was unsatisfactory because of adhesions. The retroperitoneal tissues, the intestinal tract, and the liver were normal. The uterus was broad and soft. Both ovaries contained cysts. The tubes had been removed previously. Total abdominal hysterectomy was performed without difficulty.

Pathologic examination of a specimen of the tissues removed disclosed a polypoid, Grade 4 adenocarcinoma, 8 by 5 by 2.5 cm., in the left cavity of a uterus septus. The malignant process had penetrated the uterine wall to a depth of 5 mm. A single fibromyoma, 1 cm. in diameter, was present in the uterine wall. Examination of the cervix showed chronic cervicitis and marked squamous-cell metaplasia. The right ovary was cystic; a 2 cm. cyst of the corpus luteum was found on the left.

The postoperative course was uneventful, and the patient was discharged from the hospital on the eleventh postoperative day.

Roentgen irradiation was administered because of the high grade of the lesion, and the partial penetration of the uterine wall by the lesion.

This patient was last observed in July, 1952, three years after the operation, at which time she was found to have metastatic processes in the lungs. These lesions were reportedly treated elsewhere by roentgen irradiation.

CASE 2.—A white woman, 36 years old, presented herself at the clinic in January, 1948, for evaluation of a recently irradiated, Grade 1 papillary adenocarcinoma of the uterine fundus and severe factitial proctitis.

Minimal vaginal spotting had developed during the first trimester of a pregnancy in 1945, and had subsided after the injection of hormones. Postpartum bleeding subsided spontaneously three weeks after a normal delivery in July, 1946, but recurred for a few days three weeks later. Menses were regular and normal until July, 1947, when vaginal spotting again recurred. Dilatation and curettage were performed, disclosing a Grade 1 papillary adenocarcinoma. The patient received intensive roentgen therapy and intrauterine radium irradiation, after which symptoms developed from irradiation proctitis.

When this patient was examined in January, 1948, her weight had decreased from 145 to 116 pounds. The systolic blood pressure was 120 and diastolic, 76. The skin of the abdominal wall was thickened, indurated, inelastic, and deeply tanned as a result of roentgen irradiation. The vaginal walls were smooth and atrophic. There was a firm, white, elevated area on the posterior lip of the cervix which was diagnosed by biopsy as being an effect of irradiation. There was nothing to suggest recurrence of activity of the malignant process.

Proctoscopic examination showed an irradiation slough extending from 8 to 16 cm. above the dentate margin. The lumen in this area was contracted to 1 cm.

The value for hemoglobin was 11.4 Gm. per 100 c.c. of blood, and the results of urinalysis were normal, as were those of serologic tests. Roentgenograms of the thorax disclosed nothing abnormal.

A clinical diagnosis of postirradiation carcinoma of the uterine fundus and factitial proctitis with rectal stenosis was made.

Because of the marked reaction of the tissues to irradiation, it was felt wisest to defer surgical correction, and a medical regime was outlined.

The condition of the patient was followed at frequent intervals. In February, 1948, a rectovaginal fistula developed. Vaginal and rectal bleeding occurred on four occasions between March 29 and April 22, 1948, and during the last episode 2,000 c.c. of blood for replacement was required.

Transverse loop colostomy was performed in May, 1948. During the ensuing three years there was gradual improvement in the general health of the patient, and in the condition of the tissues of the abdominal wall and pelvis. In May, 1951, the situation had become sufficiently stabilized for surgical correction to be advised for the rectovaginal fistula and the rectal stenosis. Operation was accepted.

At laparotomy on June 2, 1951, the ileum, peritoneum, and sigmoid were found to be thickened. A rectovaginal fistula 1 cm. in diameter was situated just below the cervix. The uterus was atrophic and mobile. Total abdominal hysterectomy, low anterior resection of the stenosed rectum, and resection of the fistula were performed. Continuity of the colon was restored three months later.

Pathologic examination showed the uterus to be markedly atrophic, bicornate, and containing no residual carcinoma. Chronic cervicitis and bilateral chronic salpingitis and oophoritis were noted.

CASE 3.—A white woman, 60 years old, presented herself at the clinic in April, 1939, because of persistent postmenopausal bleeding of a year's duration. There had been no pregnancies during twenty-one years of marriage. Menopause had occurred at the age of 54. Dilatation and curettage had been carried out elsewhere in November, 1938, which resulted in a diagnosis of chronic cervicitis and inflammatory polyps. The injection of hormones produced no benefit, and the bleeding continued to the time of the patient's admission. Cholecystectomy for gallstones had been performed in 1935, the surgeon reporting that there was no palpable pelvic abnormality.

Physical examination at the time of the admission in 1939 revealed no abnormalities other than a pelvic mass the size of a grapefruit. The vagina was contracted about the cervix, which was difficult to visualize. Examination with the patient anesthetized re-

portedly revealed a normal pelvis. The cervix was buried because of the overlapping of the vaginal vault. Dilatation and curettage showed atrophic endometrium, with no evidence of malignancy. It was felt that the bleeding had been on the basis of senile vaginitis, and the use of estrone suppositories was advised. Re-examination was to be performed within six months, if the bleeding continued.

The patient returned to the clinic in March, 1940, with a history of continued spotting. Hormone therapy had been continued at home, without benefit. During the two weeks prior to this admission, the patient had noted a tender mass in the lower part of the pelvis. The remainder of the history was not significant. The patient was apparently healthy, and weighed 147 pounds, without evidence of recent loss of weight. At vaginal examination, blood was seen on the vulva, but none was present in the vagina. There was a large, tender mass in the right part of the pelvic cavity.

The value for hemoglobin was 11.6 Gm. per 100 c.c. of blood. Erythrocytes numbered 4.53 million per cubic millimeter of blood. Results of urinalysis, serologic tests, and roentgenologic examination of the thorax were recorded as negative.

A clinical diagnosis of an ovarian malignant process with a secondary inflammatory process was entertained and exploration was advised and accepted.

On March 16, 1940, preliminary dilatation and curettage were performed. A small opening was found in the vagina about 1 inch proximal to the urethral orifice. This opening led posteriorly for about 5 or 6 inches; when it was enlarged, it was found to be entirely lined with vaginal mucous membrane, representing complete reduplication of the vagina. A complete cervix was present in this cavity, separate from that in the normal vaginal cavity. Curettage through the second cervix produced tissue which was diagnosed as adenocarcinoma, Grade 2.

Laparotomy was immediately performed. When the abdomen was opened, a ruptured, gangrenous, twisted cystadenocarcinoma of the right ovary was found which was collapsed, but which had been approximately the size of a small grapefruit. There was complete duplication of the uterus and cervix, the right one being atrophic and small, whereas the left was definitely enlarged and about twice the size of the right. There were only the usual tubes and ovaries. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. On further exploration, a nodule was found in the distal segment of the ileum. This nodule was removed; the pathologist's report identified it as a carcinoid tumor.

Pathologic examination of the removed specimen disclosed a Grade 2 adenocarcinoma which involved the dilated left horn of a completely double uterus, invading the muscle to a depth of 5 mm. The right ovary contained a hemorrhagic, necrotic, multilocular Grade 2 papillary intracystic cystadenocarcinoma approximately 15 cm. in diameter.

The patient received intensive roentgenologic and radium therapy after this operation, and was reported as being well, with no evidence of recurrences, in 1951.

Comment

During the five-year interval from 1950 to 1955, more than 4,500 hysterectomies were performed at the Mayo Clinic for causes other than malignancy. In some 4,000 of these cases, a pathologic diagnosis of fibromyomatosis uteri had been made, or the hysterectomy had been performed because of prolapse. In reviewing the records of this group of patients, we found 5 in whom some degree of reduplication of the uterus had been noted, an incidence of 1 in 800. This appears to confirm the opinion of Hoffman,[10] Steinberg,[11] and others that the incidence of 1 in 1,500, noted by Smith[12] among pregnant patients, is low, since many patients with these anomalies apparently have sterility problems.

In the ten-year period, 1945 to 1955, hysterectomy was performed at the Mayo Clinic for 691 patients who had adenocarcinoma of the uterine fundus. A double uterus was present in 2 of these specimens, an incidence of 1 in 345.

During this same period, hysterectomy had been performed for 633 patients who had carcinoma of the cervix, including carcinoma in situ. In one of these, a congenital abnormality also was found. This case has been reported in detail elsewhere.[13]

It may appear, on the basis of these statistics, that a malignant process is more likely to occur in a congenitally malformed uterus than in one which is normal in development, but because of the small number of cases included in the series, no such conclusion should be reached. The occurrence of a malignant process in a double uterus is probably coincidental.

It is generally accepted that the incidence of sterility is greater among such patients as the ones in our 3 cases. Strassmann[14] noted an incidence of term deliveries of only 25 per cent among those becoming pregnant. It is of interest that 2 of our 3 patients had had normal pregnancies with a normal term delivery in each instance.

Case 3 is of special significance, because of the simultaneous occurrence of three separate malignant processes, the difficulties in diagnosis which arise in uterine and vaginal duplication, and the extremely satisfactory survival period after therapy. The patient had had dilatation and curettage performed three times over a period of two years for the same symptoms, and the diagnosis of malignant involvement was made only on the last attempt, when the second uterus was identified and was found to be the source of the bleeding.

Summary and Conclusions

Three cases in which adenocarcinoma occurred in a double uterus have been presented.

The observed incidence of congenital duplication of the uterus at the Mayo Clinic in hysterectomies carried out for malignant involvement is 1 in 300, and in hysterectomies for benign conditions is 1 in 800. The small number of patients with congenital duplication encountered prevents conclusions as to the real effect of the anomaly on the future development of uterine malignancy.

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THE MANAGEMENT OF NONSPECIFIC VULVITIS IN CHILDREN

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MOST of the available literature on vulvitis and vulvovaginitis in children still deals with that caused by gonorrheal infection. This is a familiar subject but, with the widespread use of antibiotics, more and more children presenting themselves with vulvitis show negative cultures.

The normal characteristics of the immature vulvovaginal tract include a thin-walled epithelial surface, the cells of which secrete minimal amounts of glycogen which is broken down into lactic acid. As a result, there is a high pH, 7.0 or 8.0, as compared to that of the mature state. The bacterial flora are different, especially in the relative absence of Döderlein's bacillus which characteristically thrives on lactic acid in the adult vaginal tract. The normal smear contains vaginal epithelial cells but no pus cells. Endocervicitis per se is rarely seen in the child, since there are only rudimentary cervical glands.

Nonspecific vulvitis and vulvovaginitis are generally, if not always, due to an exaggeration of the normal hypoestrogenism of childhood, resulting in a true senile vaginitis.[1] In support of this etiology is the finding of leukoplakia and, rarely, even kraurosis in some of these children.[2]

The standard treatment for this condition was first that of gonorrheal vulvovaginitis, on the theory that many of these cases were simply gonorrheal infections not demonstrable on culture.[3] The diagnostic characteristics of this "senile" vaginitis are thin, watery, yellowish discharge, slightly reddened, sore or itchy vulva, adhesions between the labia minora, and pale atrophic vaginal wall. As this was recognized, the local use of estrogen suppositories and cream became popular. In cases with severe and dense adhesive sealing across the vestibule surgical intervention has been advised.[4]

All these therapeutic regimes present a certain amount of psychic and physical trauma to the child by involving the parent and the gynecologist in procedures usually accompanied by pain, with consequent fear and resistance on the part of the child, over some period of time. In addition to this direct effect, we have the normal response of the immature female from age 3 to puberty, interpreting even light tactile stimuli in the genital area by another person as pain, fear, or anger. This is a sidetracking of the adult sensory responses from the genital area which may represent a natural protective mechanism.[5] If this is aggravated so as to become persistent after puberty, it may present a definite negative factor in later sexual adjustments. Last, there are the complex and unreasonable reactions of the parents, especially the

mother who generally takes direct responsibility for the treatment, to the presence of genital pathology in the child. These reactions, which take the form of fear, shame, or horror, may easily be passed on to the child.[6]

Fig. 1.

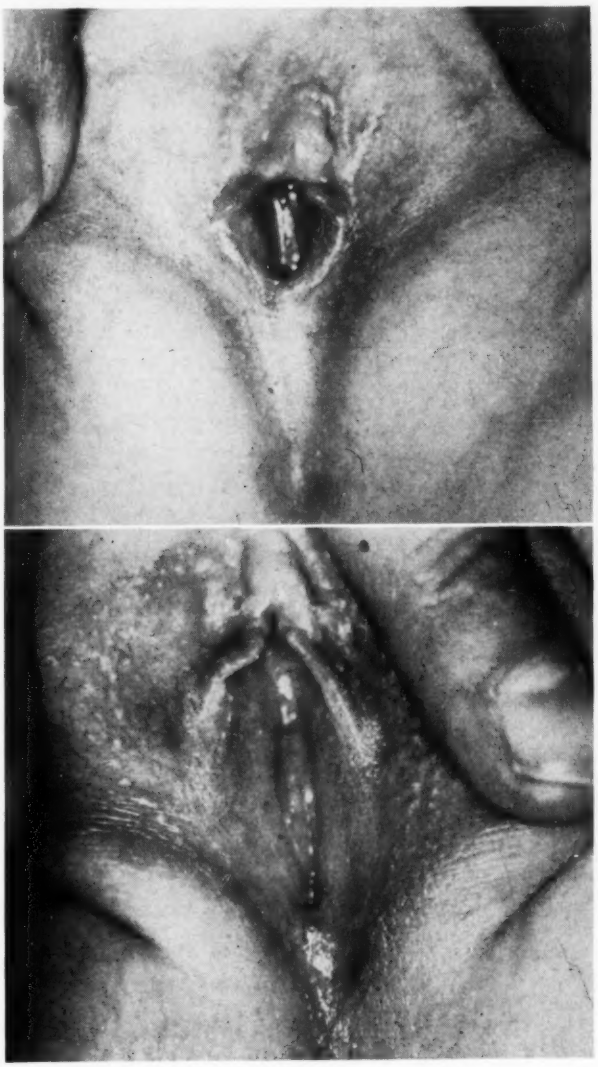

Fig. 2.

Fig. 1.—S. T. Adhesive vulvitis. Before treatment.
Fig. 2.—S. T. One month after beginning treatment.

We wish to report two cases in which local manipulations and surgery were avoided and excellent results obtained by the oral administration of estrogens. The agent was enteric-coated diethylstilbestrol in the dosage of 0.1 or 0.25 mg. daily for ten to fourteen days, or until complete lysis of the ad-

hesions occurred, followed by a tablet every other or every third night for an additional month or two to ensure against recurrence. We have found this treatment to have been completely effective (Figs. 1 and 2).

In one child, R. P., aged 7, we had initially felt that the density of the adhesions would require surgery and had given the medication as a preoperative measure. The other child, S. T., aged 4, had had many types of therapy over a period of three years with no lasting success until oral estrogens were tried. Each child has been free of recurrence now for a year.

The only side effects in each child were slight darkening and enlargement of the nipples and areolae and a fine scanty growth of pubic hair. These effects disappeared after a few months and were never marked enough to cause the children concern. Since the enteric-coated tablets are small, red, and candy covered, we encountered no difficulty in persuading the children to take them. The parents, too, found the condition, the therapy, and the minimal side effects readily acceptable.

In conclusion, we suggest small oral doses of enteric-coated diethylstilbestrol as a simple and effective therapeutic measure for hypoestrogenic adhesive vulvitis in children between the age of 3 years and puberty.

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MEMBRANOUS DYSMENORRHEA

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THE classic case of membranous dysmenorrhea is one in which a complete cast of the uterine cavity is expelled at each period with considerable pain. The first recorded description is probably that of Morgagni[7] in the seventeenth century. This condition is more common in infertile women,[2] is apparently not of inflammatory origin, and, in the past fifty years, there has been no significant relationship with exanthematous diseases.

If one limits the term "membranous dysmenorrhea" to those cases in which an *entire* cast is expelled during menses, it is a very infrequent gynecological complaint. Shedding of parts of a cast probably occurs more often than we recognize since shreds of membranes frequently can be found in persons with ordinary dysmenorrhea and in women without dysmenorrhea.[14]

The term "exfoliative endometritis" was recommended by Morse[8] in 1878 since dysmenorrhea is not necessary to the diagnosis. The disease is not a true endometritis, however, and the term "membranous dysmenorrhea" has persisted since it was first suggested by Oldham[9] in 1846.

The diagnosis usually can be made clinically, especially if the patient has saved a specimen of the cast. The cast should be examined microscopically, however, to rule out decidual casts and vaginal casts, that is, fragments of vaginal epithelium often found in an exfoliative vaginitis. Typical decidual casts are considerably larger in all dimensions and are more vascular than endometrial casts.

It was stated by Elizabeth Morse[8] in 1907 that the "etiology and pathogenesis of the condition are obscure and the treatment has been attended with little success"; unfortunately, the statement can be reiterated today.

At one time it was postulated that membranous dysmenorrhea might be a pregnancy of a few days. Other etiological suggestions have been: low quantities of tryptic ferment[4]; incomplete disintegration of the endometrium due to abnormal vascular changes[6]; interstitial hemorrhages in the spongiosa layer[10]; and result of an exanthematous disease or diabetes.[11] Wodon and Cordier[14] made careful histological studies of several casts and reported that there was usually a poor progestational effect. They found no abnormal leukocytic infiltration such as that associated with endometritis, and deciduous transformation of the endometrium was not a consistent finding. They found decidual reactions in endometrial fragments collected from women with normal menstrual periods as frequently as in fragments from dysmenorrheic women.

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The severe pain associated with the passage of an endometrial cast is unlike the moderate discomfort experienced during the passage of a decidual cast of ectopic gestation. Davis[3] feels that the detachment of the endometrium may be the result rather than the cause of the exaggerated uterine contractions.

Membranous dysmenorrhea may occur because of abrupt withdrawal of hormonal support, causing profound and prolonged ischemia; the resultant necrobiosis and capillary extravasation would separate the functionalis portion of the endometrium from the stratum basalis, and, if in toto separation occurs, a cast would be formed. That progesterone withdrawal is important seems to be evident by the inhibition of the syndrome when estrogen-withdrawal bleeding is produced.

The treatment usually adopted initially is curettage, which gives temporary relief; that is, after one or two "normal" periods, the patient again passes a cast of the uterine cavity. Presacral neurectomy was permanently successful in one case reported.[10] In a study of one patient from 1941 to 1944, Risolia and Triaca[10] of Argentina found that a bovine endometrial extract, originally developed in the U.S.S.R., was more efficacious than small doses of anterior pituitary extract, estrogens, and progesterone. They were not able to mitigate the pain completely, however. After their patient became pregnant in 1944, she had no further difficulties. Wodon and Cordier felt that there was an absence of the normally present intense vasoconstriction preceding menstruation; therefore, they recommended ergotamine as well as testosterone, the latter "to limit the growth of the spiral arterioles." Jefferies[5] was successful in the treatment of one case using a relatively inert ovarian extract combined with intrapelvic diathermy. Hazay and Rechnitz[4] were impressed with the poor development of the endometrial glands of casts extruded by five patients, and they successfully treated these women by administering progesterone during the premenstrual phase. Four of these five women subsequently became pregnant.

Case History

The patient was an asthenic, well-developed, 29-year-old white housewife who had been married twelve years and had never been pregnant. The following is excerpted from her letter requesting an appointment. "Each month I have a piece of flesh, like liver, pass from me during my period. It always passes 36 hours from the time that I start menstruating and it makes hard labor pains until after it passes. . . ." She had experienced this syndrome at practically every period since 1949. The onset of the condition was not preceded by any exanthema or other disease. On admission to the clinic in February, 1954, she brought four specimens of casts which she had preserved in alcohol. The menarche was at age 13 and before 1949 her menstrual history was normal with a 30 day cycle and a 5 day flow without pain. The patient had had an appendectomy at age 14 and in January, 1950, part of the right ovary was resected and several ovarian cysts were punctured. In March, 1953, a curettage was performed. Neither of these operations altered the pattern of her dysmenorrhea. Since 1951 she had experienced loss of libido and dyspareunia. The remainder of the patient's past history and the review of systems were noncontributory. General physical and pelvic examinations were entirely within normal limits. The urine showed no sugar or albumin and appeared normal microscopically. There was no anemia, the

blood differential was normal, the VDRL (cardiolipin) test was negative, the basal metabolic rate was minus 9 per cent, and the fasting blood sugar was 80 mg. per cent. On one occasion she had a white blood count of 13,000.

On gross examination the casts submitted by the patient had the form of the uterine cavity: a triangular sac with rounded appendages, approximately 1 mm. in length, at the sites of the tubal openings. The surface was smooth and reddish gray (alcohol fixed) and the whole cast was about 4 mm. thick at its thickest portion. Williams'[13] paper contains an illustration of a perfect cast which is almost identical to the casts submitted by this patient. Microscopically, the section of the cast showed endometrial glands in a fibrinous and cellular vascular stroma. Some of the glands showed columnar epithelium with basally located nuclei and subnuclear vacuoles.

The patient was treated with 60 mg. of thyroid daily during the entire fourteen-month period she was studied. During the first menstrual cycle she was given three 10 mg. buccal tablets of testosterone daily for five days preceding her period, but there was no alteration in the dysmenorrhea. A spasmolytic, dioxolane, had no effect on the severity of the dysmenorrhea when administered prior to the menses and during the menses in doses of 0.5 Gm. four times daily. The patient was then given 5.0 mg. of stilbestrol daily for 21 days starting on the third day of her cycle; painless vaginal bleeding occurred 7 days after the last stilbestrol tablet was taken and she did not extrude a cast. Stilbestrol nauseated the patient, however, and ethinyl estradiol,* 0.5 mg., was substituted.

After three cycles using ethinyl estradiol from the third to the twenty-third day of her cycle, the patient was allowed to have periods without pituitary suppression and again no casts were passed. After six months with only thyroid as medication, the patient passed a cast, but again responded to suppressive therapy. She has now been followed for over two years.

Summary

Membranous dysmenorrhea is a rare condition in which a complete cast of the uterine cavity is expelled with pain during a menstrual period. Its etiology is obscure, but there seems to be a relationship to the estrogen-progesterone balance.

A case is reported with a fourteen-month follow-up in which suppression of the pituitary with large doses of ethinyl estradiol or stilbestrol apparently was effective in the treatment of membranous dysmenorrhea. The patient had been suffering from the condition for four years prior to this method of treatment.

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*The ethinyl estradiol used in this study was supplied by the Schering Corporation, Bloomfield, N. J., as Estinyl.

MASSIVE RETROPERITONEAL HEMORRHAGE COMPLICATING PREGNANCY

Case Report

WILLIAM D. CHAMBLIN, M.D., AND WALLACE C. MARINE, M.D.,*
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ALTHOUGH massive retroperitoneal hemorrhage as a complication of pregnancy has been occasionally reported,[2, 5] it is rare enough never to be encountered in the average obstetrical practice. In support of its rarity, only ten cases of such hemorrhage have been reported in the literature during the past thirty-five years.[1, 3, 4] Most of these were due to rupture of the renal, splenic, or hemorrhoidal vessels through aneurysmal dilatations, although in several cases the exact site of the bleeding was unknown. Death occurred in six of these reported cases.

Confronted with a patient at term with concealed hemorrhage and shock, one would first consider abruptio placentae or uterine rupture. In addition, retroperitoneal hemorrhage, from whatever origin, can simulate either of these conditions, confusing the over-all picture and creating a more serious prognosis.

Case Report

The patient was a 19-year-old white primigravida whose expected data of confinement was March 22, 1954. As a normal patient she was followed in the prenatal clinic from the first trimester of her pregnancy.

She first developed symptoms on November 27, complaining of urinary frequency, dysuria, and suprapubic discomfort. Urinalysis at this time showed 4 to 5 white blood cells per high-power field but there was no costovertebral angle tenderness. With treatment she was asymptomatic in five days.

During January she was hospitalized on two occasions because of excessive weight gain and was rehospitalized on February 5, complaining of sharp pain in the right side and right costovertebral area. Physical examination disclosed no positive findings, and urine and blood studies were normal. The patient responded to supportive treatment and the pain disappeared in six hours. Subsequent weekly clinic visits were uneventful until March 8 when the patient was seen because of vomiting. The vomiting abated with a dextrose infusion, sedation, and an antispasmodic.

The patient's final admission was the afternoon of March 9. She arrived on the ward in shock with blood pressure recorded at 70/0 and the pulse, 160. There was no peripheral edema or external bleeding. Immediate shock treatment was instituted including oxygen, dextran, and Levophed bitartrate solution, after blood had been drawn for cross matching. The blood pressure rose to 130/90 but the pulse remained 160. A urine specimen showed 3 plus albumin, high concentration, a few red cells, and 8 to 10 white blood cells.

It was necessary to send to the near-by civilian hospital for blood for the patient since her type was not readily available at the Base Hospital. In order to obtain more than one unit, blood was rushed from the nearest blood bank in a city fifty miles away.

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The patient improved somewhat, with the blood pressure maintained while awaiting the arrival of blood. It was observed that she was having regular uterine contractions and a bloody, meconium-stained vaginal discharge. Sterile vaginal examination at this time showed the cervix to be completely effaced, 3 cm. dilated, and the vertex at station plus 1. Since no heart tones were heard, fetal death was presumed. There was satisfactory relaxation of the uterus between contractions but the patient complained of continuous abdominal pain which was not localized. She was conscious and responded to questioning. A tentative diagnosis of premature separation of the placenta was made and delivery was anticipated from below while shock therapy, to which the patient was responding, was continued. The blood pressure was maintained at 130/90 without Levophed after blood was started. Re-examination two hours after admission showed the head to be at station plus 2 with only a rim of cervix remaining. The patient was taken to the delivery room with her blood pressure remaining stable and the preparations were made for delivery. Additional blood arrived and another unit was started in the other arm.

Delivery of a stillborn male infant was accomplished under pudendal anesthesia supplemented with nitrous oxide and oxygen. The placenta, intact with membranes, was expelled with minimal blood loss. Routine injections of Pitocin* and Ergotrate† were administered. No abnormalities of the placenta were noticed and there was no evidence of a placental abruption. After the uterine cavity had been explored manually and no rents discovered, the episiotomy was rapidly repaired.

Following delivery, the patient's abdomen became more distended, doughy to palpation, and, for the first time, a mass was felt in the left upper quadrant. There was a positive fluid wave elicited and all signs of intra-abdominal bleeding were present. The blood pressure had dropped to 110/100, and preparations were therefore quickly made for laparotomy.

While the patient's abdomen was being prepared, no blood pressure could be obtained in spite of the administration of blood by pressure. She died as the peritoneal cavity was opened. As the abdomen was entered, blood was seen inside the peritoneal cavity and massive retroperitoneal hemorrhage was observed around the left kidney extending into the left lateral wall of the pelvis. The retroperitoneal hemorrhage had ruptured into the peritoneal cavity.

After the blood clots were removed, there was seen to be a rupture of the left kidney at its superior pole. The rupture had occurred through a cystic abscess cavity the size of a billiard ball but the exact site of the bleeding was not discovered. The renal and splenic vessels were intact.

Pathological Report.—

Gross: The pathological diagnoses included (a) massive retroperitoneal hemorrhage, (b) abscess of the left kidney with rupture, and (c) acute and chronic pyelonephritis of the left kidney. At autopsy the abnormal findings were confined to the urinary tract. The right kidney was entirely normal. The left kidney, which appeared twice normal size, was embedded in a large amount of old organized and recent blood which was estimated to be approximately 2 to 3 pints. There was no apparent capsule remaining on the kidney. The kidney weighed approximately 170 grams and at the superior pole there was a large ruptured abscess cavity 5 cm. in diameter, which contained a large amount of thick, foul-smelling material.

Microscopic: The retroperitoneal membranous tissue consisted of connective tissue and fat containing scattered dilated congested blood vessels throughout, in which there was a variable amount of hemorrhage. In all areas there were scattered neutrophils, lymphocytes, and large mononuclear cells.

Sections through the wall of the abscess showed the wall to be composed of granulation tissue which was quite vascular in most areas. Many of the blood vessels were of 200 μ diameter. Beneath the wall of the abscess there was a variable amount of necrotic tissue

*Pitocin ampules, 10 units, Parke, Davis & Company.
†Ergotrate maleate solution, 1 ampule, Eli Lilly & Company.

which bordered more normal kidney tissue. In the glomeruli there was fibrosis and the tubular epithelium was edematous and undergoing degenerative changes. Many of the tubules were dilated and hyaline casts were noted.

The left renal artery was opened, and there was no evidence of disruption in the continuity of the vessel wall. Surrounding the kidney there was, in addition to the recent blood, a large amount of thick fibrous organized clot. Following removal of the blood clot, it was evident that there was penetration of the blood into the iliopsoas muscles and the other muscle masses up to and involving the diaphragm and down the left lateral wall of the pelvis. There was also a large rent in the posterior peritoneum where the blood extravasated into the abdominal cavity. Both the bladder and the uterus were normal. Cultures were made from the kidney abscess and no organisms were isolated.

Comment

The attending physicians in this case were unable to establish a diagnosis until the uterus was emptied. Review of the pelvimetry films failed to show abnormalities. At no time in the patient's prenatal course were there indications of renal affliction of such a serious nature. At autopsy, however, it was obvious that there had been bleeding from the left kidney over a period of time prior to the final fatal hemorrhage. This was substantiated by the consistency and partial organization of the blood clot surrounding the kidney. Although there had been bleeding prior to the onset of the labor, it can be deduced that, with the traumatic change in intra-abdominal pressure during labor, hemorrhage increased. The full uterus obviously acted as a tamponade to the bleeding area in the left kidney, then, as the stillborn infant was delivered and the intra-abdominal pressure greatly decreased, the bleeding increased and speeded the exsanguination of the patient.

The suggestion of a blood dyscrasia as the cause of such a massive hemorrhage is a hypothetical one. It can be assumed that with blood vessels the size of those discovered in the peripheral walls of the abscess, fatal hemorrhage might occur in the absence of any hematological abnormality.

In conclusion it must be emphasized that retroperitoneal hemorrhage complicating pregnancy demands early diagnosis. If not considered and properly managed, a maternal death is the inevitable outcome.

Summary

A case report of massive retroperitoneal hemorrhage due to rupture of the superior pole of the left kidney through an abscess cavity in a pregnant patient near term is presented. Neither the mother nor the infant survived. The prognosis is generally poor in this type of overwhelming hemorrhage during pregnancy.

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A NEW AND IMPROVED METHOD FOR DELIVERY OF THE PLACENTA

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THE following method of management of the third stage of labor, which I have used in over 300 consecutive vaginal deliveries, appears to offer certain advantages over other standard current procedures. It has been found especially advantageous in reducing the duration of the third stage and minimizing blood loss during this interval.

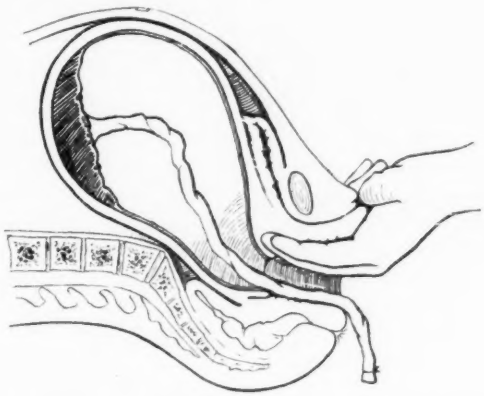

Fig. 1.—Index and middle fingers held firmly in anterior fornix.

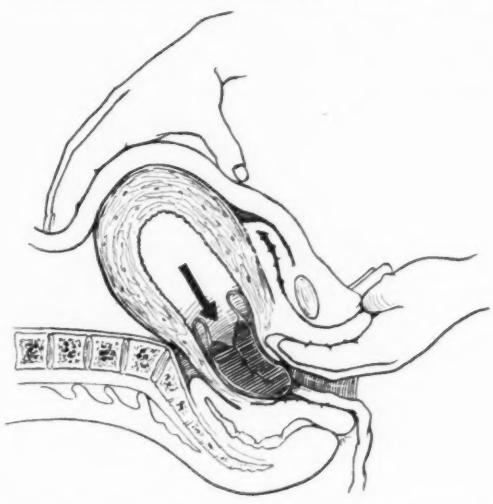

Fig. 2.—Cervix held up, out of lower birth canal, while the contracted fundus is held firmly compressed.

*Markle Scholar in Medical Science.

Immediately following delivery of the infant, the index and middle fingers of one hand are inserted into the vagina, anterior to the cervix, with the finger tips pressed firmly into the anterior fornix (Fig. 1). This helps support the uterus and keeps the cervix from protruding out through the vagina. With the other hand, the uterine fundus is gently massaged through the abdominal wall to aid uterine contraction. As soon as the fundus has contracted and is globular in contour, it is firmly compressed with the abdominal hand. This almost invariably dislodges the placenta from the fundus to the lower uterine segment or upper vagina, as shown in Fig. 2. Removal of the organ is then completed by grasping and withdrawing it with the intravaginal hand, while the corpus is held up out of the lower pelvis by the other hand, as depicted in Fig. 3. An oxytocic drug may be given as desired. Perineal repair is carried out after delivery of the placenta.

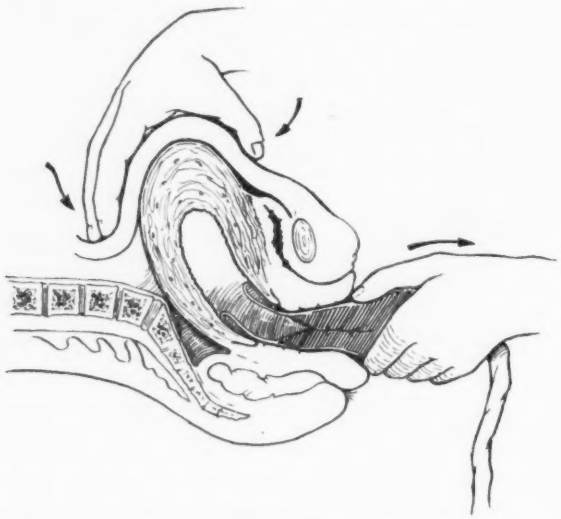

Fig. 3.—Traction is made on the placenta while the uterus is held out of the pelvis.

By this method the forces of pressure and counterpressure are exerted on the uterus. This results in a more effective expulsive action at the fundus with less strain on the supporting uterine ligaments.

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Selected Abstracts*

The American Journal of Surgery

Vol. 90, No. 2, August, 1955.

*Henriksen, E.: Endometriosis, p. 331.

Henriksen: Endometriosis, p. 331.

The author presents a review of 1,000 cases of proved endometriosis with a discussion of symptomatology, diagnosis, location, and treatment. He reiterates the several theories of the origin of endometriosis, but states that the complex nature of the disease is not fully understood. The commonly stated signs and symptoms of the disease were present in only 43 per cent of his cases. A good rectopelvic examination plus history and not just a history of progressive acquired dysmenorrhea is necessary for proper diagnosis.

Dr. Henriksen notes that involvement of the bowel occurs often enough to be considered as an etiological factor for rectal bleeding and also for obstruction of the small bowel. An acute abdominal crisis resulted from perforation of the sigmoid and in eight cases from rupture of an ovarian cyst of endometrial origin.

He then lists less common locations for endometriosis, such as lymph nodes, umbilicus, bladder, cervix, episiotomy scar, etc.

The author further shows that although 82 per cent of his patients were in the 30 to 45 year group, the disease occurred in patients as young as 16 years and as old as 83.

The article ends with a discussion of treatment and emphasis on conservative management, particularly in the childbearing period.

ROBERT C. KNAPP, M.D.

Archives of Surgery

Vol. 70, May, 1955.

*Taylor, E. Stewart: Adrenal-cortical Hyperplasia and Virilization of the Female, p. 701.

Taylor: Adrenal-cortical Hyperplasia and Virilization of the Female, p. 701.

The author presents a classification of this syndrome with division into congenital and acquired types. A discussion of the levels of 17-ketosteroid excretion in each category follows with consideration of the role of cortisone therapy in the reduction of its excess, and with alleviation of symptoms.

This report then discusses the theoretical considerations concerned with the hyperplasia of the reticularis zone of the adrenal cortex, presumably the site of the production of

*Titles preceded by an asterisk are abstracted below.

androgens responsible for virilization. This is believed to be secondary to primary atrophy of the fasciculata zone responsible for cortisone production, thus permitting unopposed ACTH stimulation of the reticularis zone to hyperplasia.

Surgical treatment of the external genitals and adrenals is briefly reviewed.

S. B. GUSBERG, M.D.

Archivo di obstetricia e ginecologia (Naples)

Vol. 60, No. 3, May-June, 1955.

La Torretta, G.: Urinary Protein Values in Toxemia, p. 137.

Danessino, V., and Martella, E.: Modern Concepts of the Function of the Corpora Cavernosa of the Vagina and Clitoris, p. 150.

Martella, E.: The Nuclear/Nucleolar (N/n) Ratio in Desquamated Cells of the Female Genital Tract, p. 163.

Longo, G.: Contributions to the Study of Hormonal Allergy, p. 179.

Berlingieri, D.: Morphology and Evolution of the Bregmatic Fontanel in the Newborn of Sardinia, p. 195.

Cerasuolo, G., and Magri, E.: The Antihyaluronidase Activity of the Blood in Toxemia, p. 206.

Vol. 60, No. 4, July-August, 1955.

Tortora, M.: Rh-Hr Factor in Exclusion of Paternity, p. 217.

*Tortora, M.: Primary Ovarian Pregnancy, p. 221.

Mutti, P.: The Action of the Oxytocic Hormone of the Posterior Pituitary on the Peripheral Blood of Female Rabbits, p. 226.

Danessino, V.: The Process of Contraction in the Human Uterus, p. 248.

La Torretta, G.: The Antistreptolysin Titer in Maternal Blood, Fetal Blood and Colostrum, p. 259.

La Torretta, G.: Immunization Against the D^u Factor Following a Pregnancy, p. 266.

La Torretta, G.: The Pattern of the Blood Proteins in the Newborn. Electrophoretic Studies, p. 270.

Martella, E.: Significant Biological Levels of the Chorionic Gonadotrophins Tested in the Male Frog, p. 282.

Martella, E.: Afibrinogenemia, p. 286.

Colscurci, A.: The Action of Desoxycorticosterone and Testosterone on the Symphysis Pubis in Oophorectomized Guinea Pigs, p. 300.

Tortora: Primary Ovarian Pregnancy, p. 221.

The author reports a case of ectopic pregnancy in a 30-year-old Italian woman, para i-0-i-i, which he feels fulfills Spiegelberg's criteria for the diagnosis of a primary ovarian pregnancy. Prior to operation the case had been diagnosed and treated as inflammation, appendicitis, threatened abortion, and ruptured tubal pregnancy. A subtotal hysterectomy and bilateral salpingo-oophorectomy were performed.

FRANCIS B. O'BRIEN, M.D.

Deutsche Medizinische Wochenschrift

Vol. 80, No. 17, April 29, 1955.

Stefenelli, N., and Wewalka, F.: A Contribution to the Differential Diagnosis of the Distended Abdomen, p. 675.

Schmiedt, E.: The Treatment of Bladder Irritation, p. 687.

Vol. 80, No. 18, May 6, 1955.

Schmauss, A. K.: The Treatment of Carcinoma of the Breast With Hormones, p. 729.

Vol. 80, No. 21, May 27, 1955.

Dietrich, A.: Cancer and Changing Scientific Concepts, p. 807.
Hackmann, C.: Antibiotics as Antineoplastic Agents, p. 812.

Vol. 80, No. 22, June 3, 1955.

Rieckert, P.: The Development of Necrotizing Colitides During Antibiotic Therapy, p. 855.

Vol. 80, No. 23, June 10, 1955.

Soiva, K.: Active Control of the Postpartum Period, p. 889.

Vol. 80, No. 24, June 17, 1955.

Koettgen, U., Braun, E., and Friedberg, V.: Preserving Human Milk by Cold Dessication, p. 923.

Vol. 80, No. 25, June 24, 1955.

*Philipp, E.: Menstrual Disorders in Young Girls, p. 947.

Philipp: Menstrual Disorders in Young Girls, p. 947.

Menstrual disturbances in young girls can have a multiplicity of causes. It is extremely important to make a diagnosis before starting treatment and to avoid protracted, unjustified hormone therapy. Malformations like imperforate hymen or various degrees of genital aplasia can frequently be diagnosed quite simply. There is often hormonal dysfunction either on an ovarian basis or an imbalance of the pituitary-ovarian axis. In the former, gonadotropin levels are high and estrogen administration can produce withdrawal bleeding. In some cases, the Stein-Leventhal syndrome is present and can be treated by wedge resection. The diagnosis and treatment of hermaphrodites are mentioned in passing. Diagnostic aids in apparently normal girls are discussed such as body measurements and x-rays to show closure of epiphyses, basal temperature, therapeutic test of cyclic therapy, determination of gonadotropin levels, 17-ketosteroid levels, and vaginal cytology and endometrial biopsy. It is emphasized that the adrenal cortex plays an important part in sexual development.

WALTER F. TAUBER, M.D.

Fertility and Sterility

Vol. 6, January-February, 1955.

Goldziehr, Joseph W.: Present Concepts of Menstrual Physiology: A Critical Appraisal, p. 1.
Perloff, William H., Schultz, Julius, Farris, Edmond J., and Balin, Howard: Some Aspects of the Chemical Nature of Human Ovarian Follicular Fluid, p. 11.
Gillam, John S.: Study of the Inadequate Secretion Phase Endometrium, p. 18.
Hotchkiss, Robert S., Pinto, Asdrubal Baias, and Kleegman, Sophia: Artificial Insemination With Semen Recovered From the Bladder, p. 37.
Payne, Sheldon, and Skeels, Robert F.: Testicular Biopsy: Which Infertile Patients Are Benefited? p. 48.
*Norwood, G. E.: Pregnancy After Conservative Surgery for Endometriosis: A Statistical Study, p. 51.
*Wied, George L.: Suggested Standard for Karyopyknosis: Use in Hormonal Reading of Vaginal Smears, p. 61.
Hunter, Robert G., and Henry, George W.: Cervicohysterosalpingography: Preliminary Report on a New Cannula and Technic, p. 73.

Norwood: Pregnancy After Conservative Surgery for Endometriosis, p. 51.

A statistical study was made of 54 married patients who had been subjected to conservative surgery for endometriosis.

The absolute fertility postoperatively was 94.4 per cent and it was not affected by the degree of endometriosis. Of the 54 patients, 30 had not been pregnant previous to operation. Postoperatively 63 pregnancies resulted with 42 viable offspring. A second group of 21 patients who had been pregnant previous to operation showed only a moderate increase in viable pregnancies afterward. There was a very evident drop in pregnancy wastage in the group, however.

ALVIN M. SIEGLER, M.D.

Wied: Suggested Standard for Karyopyknosis: Use in Hormonal Reading of Vaginal Smears, p. 61.

The presence of pyknotic nuclei in exfoliated, superficial squamous epithelial cells in vaginal smears is generally considered as an indication of estrogenic activity, based on the assumption that cornification of squamous epithelial cells of the vagina is a function of estrogenization.

In order to eliminate as far as possible the subjective factor in the interpretation of smears, the cytologist should use a method which objectively distinguishes pyknotic from translucent or vesicular nuclei.

The vaginal smears are prepared following the fixation and staining procedure of Papanicolaou. After fixation, staining, and mounting with balsam with a very thin coverslip, the smears are examined under a phase-contrast microscope. Due to a specific phaseoptical phenomenon, dark, dense bodies shine with a very light red color, whereas the less dark, translucent, and vesicular nuclei retain the original dark color of the stained chromatin. A low, dry objective of the microscope makes it possible to examine the 300 cells required for the count in a very short time. With the method accurate counts of the karyopyknotic index can be made readily.

ALVIN M. SIEGLER, M.D.

Vol. 6, March-April, 1955.

Riley, Gardner M., Dontas, Eugenia, and Gill, Barbara: Use of Serial Vaginal Smears in Detecting Time of Ovulation, p. 86.

*Whitelaw, M. James: What Is Normal Female Fertility? p. 103.

*MacLeod, John, Gold, Ruth Z., and McLane, Charles M.: Correlation of the Male and Female Factors in Human Infertility, p. 112.

Steinberg, Werner: Cervical Aspects in Sterility and Infertility, p. 169.

Whitelaw: What Is Normal Female Fertility? p. 103.

A study of 258 postpartum clinic and private patients between the ages of 20 and 34 was made. They were married a minimum of 24 months and were interrogated by an experienced interviewer with no forewarning and consecutively. Eight patients were excluded because of refusal to answer part of the questions. Results of these analyses showed that 15.8 per cent of all postpartum private and clinic patients conceived within one month or less of exposure; 69.6 per cent within three months of exposure; 80 per cent within six months; the remaining 20 per cent averaged from seven to fifty-one months before conception.

In the series 15 (6 per cent) patients showed totally irregular menses throughout their histories. Six (40 per cent) of the group were patients of high fertility. In reviewing the relationship of fertility to the age of the patients there was little or no falling off of fertility until the patient had passed the age of 29. The previous use of contraceptives had no effect on fertility following their omission. In the small series reported the weight of the patient did not affect her ability to conceive. It was concluded from the study that a maximum time of only six months should elapse before instituting a fertility investigation.

ALVIN M. SIEGLER, M.D.

MacLeod, Gold, and McLane: Correlation of the Male and Female Factors in Human Infertility, p. 112.

In the present study the authors have endeavored to correlate semen qualities and gynecologic disorders in the female partner with conception performance. A total of 916 couples who were known to have been trying at least one year and who had never produced a conception were studied. More or less complete information was compiled on 755 (82.4 per cent) of them. Of the 180 conceptions which occurred within one year of the first semen examination done by the authors, 48, or nearly 27 per cent of the conceptions, occurred within one month after the semen examination, and 70 per cent of them in less than 6 months. While 72 per cent of the 180 women who conceived within one year following the semen examination were under 30 years of age, the age factor was not of importance in determining whether they would conceive in one month or 12. None of the wives (14) above 40 conceived. In so far as all criteria of semen quality are concerned, male fertility showed no obvious changes between the ages of 20 and 40. The time taken to produce a conception was the criterion for measuring the degree of fertility. The gynecologic history in the age groups under and over 30 did not differ significantly. The pregnancy rate decreased sharply with increasing duration of infertility. Conception occurred in 31 per cent of the couples who had a history of infertility of one to three years' duration, in 18 per cent with three to five years', 13 per cent with five to ten years', and only 4 per cent of those who tried at least ten years conceived.

The pregnancy rate for those couples in whom the frequency of intercourse normally was less than twice weekly was lower than for those whose frequency was twice weekly or more.

In wives under the age of 30, it was found that where the fertility of both husband and wife was poor only 3 per cent of the couples conceived within the alloted period of 1 year following the semen examination but in the same age group when the fertility of the wife was poor and that of the husband good, 23 per cent conceived. Where the husband was "poor" and the wife was "good," the conception rate was 25 per cent. When the fertility of both was good the conception rate was 40 per cent, an impressively high figure.

While the husband of good fertility did much to help the wife of impaired fertility when she was under 30, he did little if she was over 30 years of age.

The article is comprehensive and should be read in its entirety.

ALVIN M. SIEGLER, M.D.

Vol. 6, May-June, 1955.

*Stein, Irving F.: The Management of Bilateral Polycystic Ovaries, p. 189.
Behrman, S. J., and Niemann, Philip: Serum Gonadotropins in Normal and Abnormal Pregnancy: 1. Quantitative and Qualitative Analysis, p. 236.
*Suzuki, Masamichi: Ovarian Function in Latent Genital Tuberculosis, p. 259.

Stein: Management of Bilateral Polycystic Ovaries, p. 189.

The diagnosis of Stein-Leventhal syndrome may be suspected in women who have infrequent menses although some complain of menometrorrhagia. All are anovulatory and therefore infertile. Some are obese and others may be hirsute. When palpation of the pelvic organs gives inconclusive information concerning the ovaries there are several alternative steps: (1) examination under anesthesia, (2) culdoscopy, (3) colpotomy, and (4) gynecography. Vaginal smears are not consistent, the basal metabolic rate is usually within normal range, the cervical mucus does not undergo the usual cyclic variation, endometrial biopsy is predominantly low to midproliferative, basal body temperature charts show monophasic curves, and the 17 ketosteroids are not usually abnormal.

Bilateral ovarian wedge resection which is advised as a treatment of choice in these cases evolved from ovarian biopsy. It was found that the operative procedure resulted in the restoration of ovarian function in cases of long-standing secondary amenorrhea. Appendectomy is not advisable at the time of wedge resection inasmuch as the incised ovary is extremely vulnerable to infection.

In view of some recent studies where a large number of cases of bilateral polycystic ovaries were associated with adenocarcinoma of the uterus it is currently advised to perform a diagnostic dilatation and curettage in the Stein-Leventhal syndrome. Those patients in whom hyperplasia of the endometrium is found should be carefully followed for the earliest recognition of endometrial carcinoma.

ALVIN M. SIEGLER, M.D.

Suzuki: Ovarian Function in Latent Genital Tuberculosis, p. 259.

A study was made of the ovarian function in 39 women with latent general tuberculosis by analysis of basal body temperature and endometrium. Ten of the patients were studied by the temperature method, 5 by the biopsy technique, and 24 women by both methods. Normal ovulatory patterns were observed in 85 per cent of the cycles studied and anovulatory patterns in approximately 13 per cent. Compared with a control group of infertility patients who were presumed to be free of tuberculosis there was found to be no greater incidence of abnormal ovarian function in the patients with the disease. An incidental finding of interest was the presence of cyclic biphasic curves in two patients with prolonged secondary amenorrhea without the occurrence of menstrual bleeding at the end of the elevated biphasic period. Evidence was presented that the amenorrhea was probably due to the extensive destruction of the endometrium by the tuberculous lesion rather than to a disturbance in ovarian function. One of the patients developed ovular menstruation following streptomycin therapy.

ALVIN M. SIEGLER, M.D.

Vol. 6, July-August, 1955.

*Shettles, Landrum B.: A Morula Stage of Human Ovum Developed in Vitro, p. 287.
*Romberg, George H.: Endometrial Aspiration Smears in the Study of Infertility; Further Observations, p. 302.
Simmons, Fred A., and Taymor, Melvin L.: Failure of Conception in 100 Completely Studied Couples: Analysis of Factors in Infertility, p. 320.
Glass, S. J., Miller, Walter, and Rosenblum, Gordon: Secretory Hypoplasia of the Endometrium, p. 344.
Kantor, Herman I., and Kamholz, Jack H.: Cyclic Endometrial Changes Without Menstruation, p. 353.
*Barlovatz, A.: Sterility in Central Africa, p. 363.
Noble, Nelle S.: Policies and Practices in Iowa Hospitals Relating to Human Sterilization, p. 375.

Shettles: A Morula Stage of Human Ovum Developed in Vitro, p. 287.

A report of the development of a human ovum to a morula stage of approximately 32 cells within 72 hours after exposure to spermatozoa in vitro was given. The ovum and follicular fluid were discharged into a sterile Petri dish to which a drop of fresh human semen and some minced fragments of Fallopian tubal mucosa were added. The ovum which developed represented the most advanced stage to which the human ovum has been seen to progress following insemination in vitro.

ALVIN M. SIEGLER, M.D.

Romberg: Endometrial Aspiration Smears in the Study of Infertility, p. 302.

A further study of the endometrium as evaluated from a new technique of endometrial aspiration smears was reported. The technique was used as a method of evaluating hormonal influences on the uterine mucosa in two cases. In three other cases cytologic alterations in the endometrium were described from the analysis of aspiration smears. Romberg states that in some problem cases where the endometrial biopsy study and basal body temperature graphs are abnormal, the endometrial smear will be useful in disclosing latent hormonal abnormalities.

ALVIN M. SIEGLER, M.D.

Barlovatz: Sterility in Central Africa, p. 363.

The study is based on 2,485 cases of sterility in African Bantu women observed in private practice between Jan. 1, 1950, and Dec. 25, 1952, at Stanleyville. The Bantu considers sterility shameful. The desire for children is strong regardless of economic and social circumstance. About 15 per cent of the patients were unmarried women. Birth control is rare. The presenting complaints of the infertile patient are cloaked by many psychosomatic complaints.

No major avitaminoses are prevelanet among the population. The over-all birth rate is in excess of 25 per thousand per year.

The common venereal diseases are all present but the most important is gonorrhea. Only 8 per cent of the males have never had the disease while about 50 per cent have had it two or more times. The local prevalence of gonorrhea does not stem from a lack of facilities for treatment but an apparent high drug resistance of the local strains. A history of the disease is present in about nine in every ten marriages and must be combated before more elaborate measures are undertaken.

About 50 per cent of the women have palpable abnormal gynecologic findings.

Tubal insufflations are performed under amyl nitrite inhalation with gradually increasing pressures until 30 or 35 cm. Hg is reached, either with the Tubingen insufflator, or with a large syringe connected with a hollow sound inserted into the uterus, the cervix being pinched tightly around the instrument. By auscultation of the abdomen it is usually possible to distinguish the sound of each tube when both are permeable and when only one is patent to determine whether it is the right or left one. Before insufflation the author suggests preliminary treatment with antibiotics; a minimum of 3 million units of penicillin is employed in apparently healthy subjects. If tubal patency is demonstrated the patient receives 2 million units of penicillin in the subsequent 3 days in addition to 12 Gm. of sulfonamide and some streptomycin. There were no fatalities recorded and less than 0.5 per cent peritoneal reactions.

Semen studies were performed on 1,025 men. There were no days of deliberate continence prior to the collection. About 11 per cent of the males were azoospermic and another 4 per cent showed extreme oligospermia. The treatment of the infertile couple is given in a very brief part of the paper. It appeared that antibiotics and tubal insufflations accounted for the majority of successful outcomes.

ALVIN M. SIEGLER, M.D.

Vol. 6, September-October, 1955.

Heiman, Marcel: Psychoanalytic Evaluation of the Problem of "One-Child Sterility," p. 405.

Behrman, S. J., and Nieman, Philip: Serum Gonadotropins in Normal and Abnormal Pregnancy: II. Function and Action of Chorionic Gonadotrophin Hormones, p. 415.

Rutherford, Robert N., and Banks, A. Lawrence: The Formation of a Private-Office Fertility Clinic, p. 422.

*Siegler, Alvin M.: Diverticulosis of the Fallopian Tubes: A Clinical and Roentgenologic Study, p. 432.

*Joel, Charles A.: The Role of Spermatozoa in Habitual Abortion, p. 459.

Siegler: Diverticulosis of the Fallopian Tubes, p. 432.

There is no unanimity of opinion concerning the proper nomenclature of this entity. It has been termed salpingitis isthmica nodosum, diverticulosis, adenomyosis, and endosalpingiosis. Four current concepts which attempt to explain the etiology and pathogenesis were presented.

From a series of 1,160 hysterosalpingograms performed on women who complained of infertility 19 cases of tubal diverticulosis were diagnosed. Only 3 patients in the group had normal term pregnancies prior to the investigation for infertility. There had been

11 spontaneous abortions and 2 ectopic tubal pregnancies. The lesion was associated with endometriosis in 2 patients, pelvic inflammatory disease in 2 patients, myoma of the uterus in 8 patients, cervical stenosis in 3 patients, and a retrodisplaced uterus in 2 patients.

The right Fallopian tube was involved in 6 instances and the left Fallopian tube in 13 cases. The lesion occurred predominantly in the isthmus. It was bilateral in one case. The affected tube was patent in 8 instances and occluded in 7. In 4 cases the patency could not be evaluated.

The x-ray picture must be differentiated from that in tuberculosis of the Fallopian tubes. Many diverticula were usually present resembling the branches of a tree. The characteristic sites were in the isthmic, isthmoampullary, and isthmocornual regions of the Fallopian tubes.

On gross examination the Fallopian tube affected by diverticulosis was characterized by the presence of a firm, thickened segment of tubal isthmus which caused either a complete occlusion of the lumen or a marked constriction of it. The nodules were located in the muscular wall of the tubes and contained nests of glandlike tissue.

THE AUTHOR.

Joel: Role of Spermatozoa in Habitual Abortion, p. 459.

An attempt was made from a study of the male partners of 114 couples to correlate morphologic abnormalities of the spermatozoa and certain types of abortion. In only six instances did the semen specimens exhibit a very high degree of pathologic changes in the spermatozoa. The six wives had normal pregnancies and deliveries in marriages contracted with other men. However, no definite conclusion can be drawn because of the small size of the family. It is not known whether a pathologic spermatozoan can fertilize and whether its cytoplasm has any function in the zygote.

Although the contribution of the male is of obvious importance, as yet no clear-cut relationship between the external morphology of the spermatozoa and abortion has been found.

ALVIN M. SIEGLER, M.D.

Journal of Clinical Endocrinology and Metabolism

Vol. 15, August, 1955.

*Davis, M. E., and Wied, G. L.: 17-Alpha-Hydroxyprogesterone-Caproate: A New Substance With Prolonged Progestational Activity. Comparison With Pure Progesterone, p. 923.

Davis and Wied: 17-Hydroxyprogesterone-Caproate: A New Substance With Prolonged Progestational Activity. Comparison With Pure Progesterone, p. 923.

Three castrated women were given 17-alpha-hydroxyprogesterone-caproate two weeks following the administration of estradiol valerate. In order to prevent the possible development of estrogen withdrawal bleeding, estradiol valerate was also given with the 17-alpha-hydroxyprogesterone-caproate. Chemically pure progesterone was substituted for the 17-alpha-hydroxyprogesterone-caproate in the experiment for a control.

By means of endometrial biopsies and vaginal smears, the authors were able to demontrate that the uterine bleeding from a secretory endometrium occurred about one week later when 17-alpha-hydroxyprogesterone-caproate was used than when progesterone was employed.

J. EDWARD HALL, M.D.

Correspondence

Further Correspondence on the Etiology of Toxemia

To the Editors:

Dr. Hofbauer's article in the February, 1956, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, p. 255, will arouse much interest among obstetricians. He appears to imply that (a) the internal secretions and abnormal products of metabolism, exchanged in the chorionic blood stream between foetus and mother, serve as a stimulus for (b) hypothalamic-pituitary-adrenal overactivity and for (c) heightened sensitivity of the arterioles consequent on hormonal outpouring.

Clinicians will note his concept of the source of foetal noradrenalin and its effects on circulation in the cord conducing to placental infarction. Morris has proved him correct in his surmise that a reduced myometrial circulation occurs in toxaemia, which may well explain the reduced blood flow through the placenta encountered. His statement that relative anaemia of the uterine wall is the result of toxaemia is an oversimplification for heightened uterine tension can bring it about, and such increases in tension have been demonstrated in pre-eclampsia.

The first part of his theme (a) is difficult to reconcile with certain observed facts, for it fails to explain the recrudescence of toxaemia during labour, after its abatement days earlier on the death of the foetus, when foetal noradrenalin could not longer be produced nor placental exchanges affected.

Cushing postulated posterior lobe activity in toxaemia claiming basophilic infiltration to have occurred. Spark produced evidence still unchallenged to deny this. With regard to vasopressin, large amounts are needed to elevate the blood pressure. Its presence has been detected by Grollman in the blood of dogs with experimental hypertension, but in quantities quite insufficient to be responsible for the level of elevation. Therefore, the mere identification of its representative component phenylalanine in the urine in pre-eclampsia can hardly be held to connote aetiological significance. Antidiuretic hormone (ADH) is also unlikely to be of prime import in the syndrome, for Dieckmann has reported toxaemia in patients suffering from diabetes insipidus.

Teel, however, did find some increase of ADH in certain toxaemic patients.

Regarding pituitary effects, controversy still rages over the aetiological implications of high gonadotrophin production in the disease; while, with regard to ACTH, its experimental exhibition by Assali in women and in monkeys during normal pregnancy has failed to provoke the toxaemia syndrome. It must be conceded, however, that aldosterone, recently so strongly suspected in the aetiology, is outside ACTH influence. The fact that aldosterone has been found in nephrosis, congestive heart failure, toxaemia, and cirrhotic ascites strongly militates against the concept that it is *primarily* responsible for the oedema in conditions of such diverse pathology, a conclusion supported by Venning's findings of the reduction of the originally high urinary levels in toxaemia, as eclampsia threatens.

Dr. Hofbauer draws attention to the increased formation, or the insufficient destruction, of noradrenalin in toxaemia, and, although its exclusively vasoconstrictor effects may appear to accord it a share in the hypertensive process, its property of provoking a marked rise in pulmonary blood pressure must deny it aetiological significance in pre-eclampsia where pulmonary hypertension is not encountered. Moore's findings also suggest that the generalised vascular resistance is not primarily dependent on autonomic vasoconstrictor tone.

It is significant that none of these naturally occurring hormones has ever been shown experimentally or in disease to excite convulsions.

The author omits consideration of a pertinent further endocrine—renin—found by Dexter and Haynes to occur in the plasma of the toxaemic; and for whose production I as well have advanced a "neuro-endocrine" mechanism—the uterorenal reflex. Renin itself can act as an antidiuretic (though not invariably in all species); it can provoke hypertension and can cause albuminuria. Both renin and hypertension can stimulate the release of ACTH while renin has been demonstrated angiographically to excite renal cortical ischaemia. Its exhibition in rats, previously sensitised by DCA and salt, results in a syndrome of oliguria, albuminuria, gross oedema, hypertension, and fits. But of supreme interest are the dramatic findings of Byrom, who, solely by Goldblatt clamping of the renal artery, provoked in rats, previously trephined and with a transparent window inserted to replace the bone removed, severe convulsions and (visualised) spasm of the cortical vessels as a result of the marked hypertension effected. Many of these animals previously nurtured on salt developed acute and massive oedema concomitantly. Removal of the clamp rapidly restored the rat to normal. Renal cortical ischaemia provoked by renin or by Goldblatt clamping reproduces the clinical picture of pre-eclampsia in its entirety. The cortical ischaemia in its turn can be evoked by the uterorenal reflex. Therapeutics in its advance must rely on these essential guideposts for direction.

Since this letter was compiled, fresh evidence has been provided by Barnes and Quilligan that the relationship between aldosterone and toxaemia is too variable to permit of it being considered a primary factor in the causation of the disease.

On request, references will be given by the author.

JOHN SOPHIAN

66, HARLEY STREET,
LONDON, W.1., ENGLAND
MARCH 26, 1956

Reply by Dr. Hofbauer

Resurrecting the view proclaimed for decades in the German literature by Gessner to the effect that no uterorenal reflex represents the fundamental etiological factor in toxemia, Sophian directs some missiles of criticism against my paper in the February issue of this JOURNAL, which created a new field of thought by dramatically high-lighting the identification in toxemia of Pitressin and noradrenalin and the markedly increased sensitivity to these hormonal principles of the arterioles as essential facets of the disorder. I undeviatingly adhere to this doctrine and am supremely confident that it initiates the full conquest of the problem.

In contrast, I find it difficult or rather impossible to follow Mr. Sophian's way of reasoning. Noradrenalin, indeed, produces renal cortical ischemia which, according to him, reproduces the clinical picture of "pre-eclampsia in its entirety." That "the cortical ischaemia can be evoked by the uterorenal reflex" has never been demonstrated in my recollection. Finally, the admonition that "therapeutics in its advances must rely on these essential guideposts for direction" I hope and pray will not lead to the resumption of Gessner's obsessive advice to resect the ureter as a therapeutic agent in severe toxemia.

J. HOFBAUER

SHERATON-GIBSON HOTEL
CINCINNATI, OHIO
MAY 22, 1956

Items

American Board of Obstetrics and Gynecology

Applications for certification (American Board of Obstetrics and Gynecology) for the 1957 Part I Examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of applications is Oct. 1, 1956.

Candidates for admission to the Examinations are required to submit with their application a plain typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application.

Application for re-examination, as well as requests for resubmission of case abstracts, must be made to the Secretary prior to Oct. 1, 1956.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office.

ROBERT L. FAULKNER, M.D., Secretary
American Board of Obstetrics and Gynecology
2105 Adelbert Road
Cleveland 6, Ohio

The following candidates were certified by the American Board of Obstetrics and Gynecology on May 20, 1956:

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Notes on the Diagnosis and Management of "Dizziness"

Ménière's Syndrome

1. Paroxysmal Whirling Vertigo. *This consists of sudden attacks of dizziness, often when the patient is at rest or asleep. The patient may feel that he himself is whirling or that fixed objects about him are whirling. The attack usually lasts for a few minutes; occasionally it is severe for weeks or subacute for months.*

2. Subtotal Hearing Loss. *Deafness will usually affect the high tones and it may be unilateral or bilateral. Sometimes the hearing loss is severe and also progressive.*

3. Tinnitus. *This is usually unilateral and present in the ear with greater hearing loss and is without a definite pattern.*

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1. Severe paroxysmal vertigo which may be of two types; either the patient feels that he is whirling or that objects about him are whirling.
2. Fluctuating subtotal hearing loss, usually affecting the higher tones, is noted at the same time as vertigo.
3. Tinnitus, usually unilateral, is associated with the deafness and dizziness.

With Ménière's syndrome there is no definite localization[2] by the Bárány (vestibular reaction) test and results of the caloric test are not diagnostic. Physical examination should rule out disease of the central nervous or cardiovascular systems before a diagnosis is made.

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1. DeWeese, D. D.: Symposium: Medical Management of Dizziness. The Importance of Accurate Diagnosis, Tr. Am. Acad. Ophth. *58*:694 (Sept.-Oct.) 1954.
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3. Queries and Minor Notes: Ménière's Syndrome, J.A.M.A., *141*:500 (Oct. 15) 1949.

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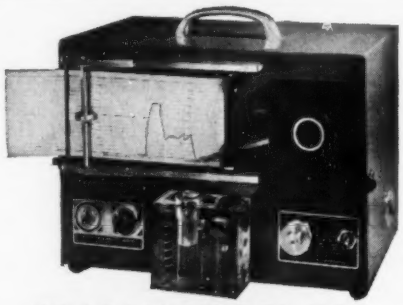

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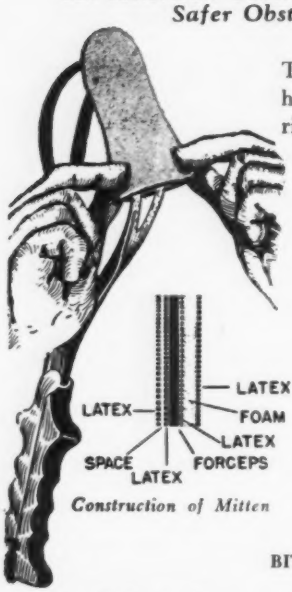

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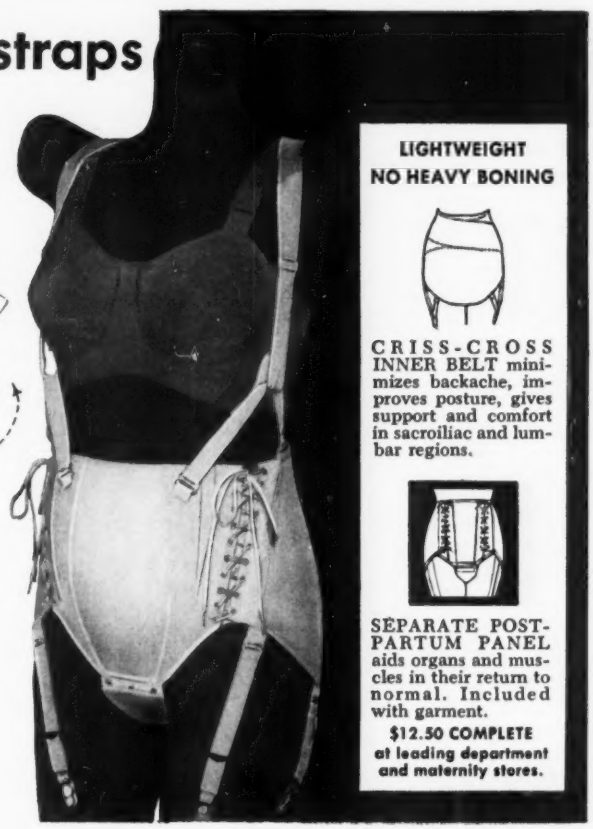

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"tails"... because the easily digested, efficiently utilized protein content of BREMIL (approximating that of breast milk) virtually eliminates excoriations due to ammonia dermatitis[1], and does not impose an excessive solute load on the immature kidney[2]

Standard Dilution

One level measure to 2 fluidounces of hot water. Mixes like a liquid. Costs no more than ordinary formulas requiring vitamin and carbohydrate supplementation. In 1-lb. tins at all drug outlets.

1. Oberman, J. W., and Burke, F. G.: M. Ann. District of Columbia 23:483, 1954. 2. Hill, L. F.: Am. J. Clin. Nutrition 3:75, 1955.

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